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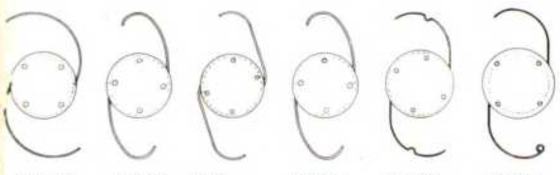

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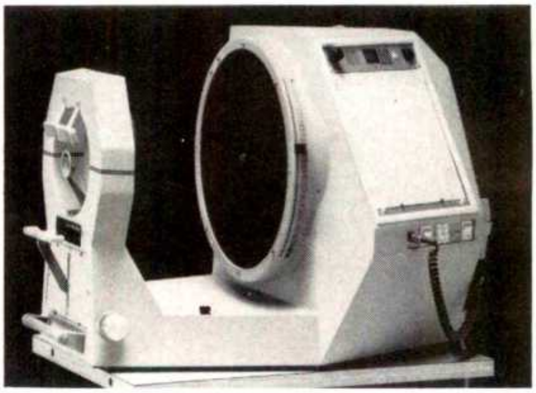

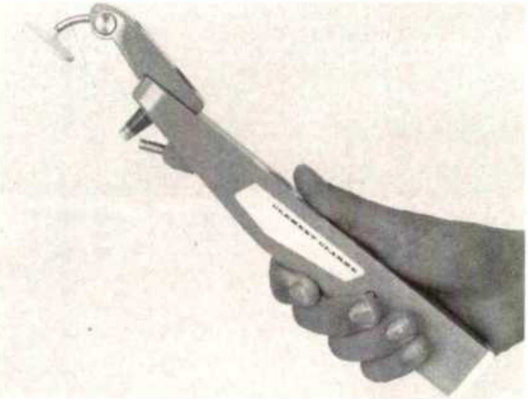

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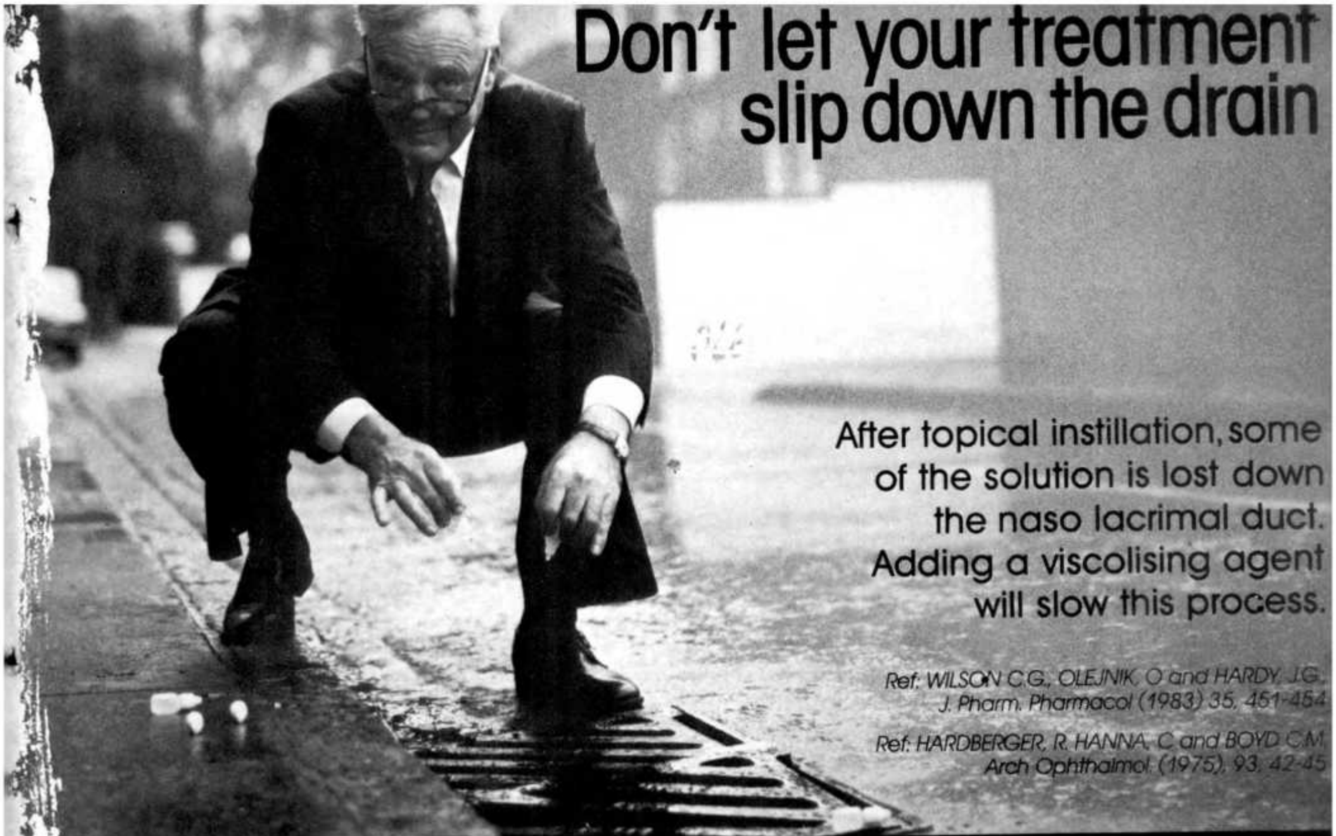

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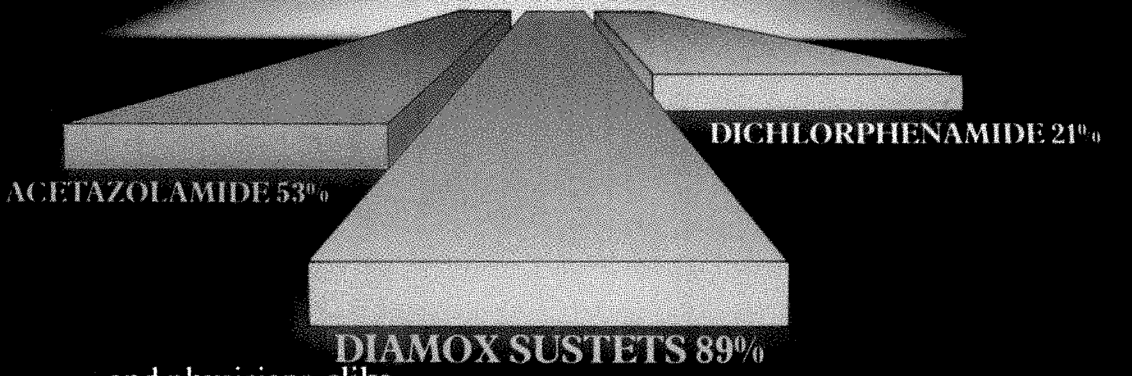

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Editorial: Herpes simplex conjunctivitis

The average clinician's attitude to conjunctivitis is affected by his background and his work-load. If he was trained many years ago and is subject to a heavy burden of work his diagnosis may tend to be based on simple clinical inspection, although he might order a swab for bacterial culture. The likely result of this will be 'no growth.' Although he may be puzzled as to why all the bacterial conjunctivitides described so abundantly in the classical texts (there are, for example, 90 pages of them in Duke-Elder's *System of Ophthalmology*[1]) are so reluctant to declare themselves on a culture plate, he will nevertheless tend to accept a moderate incidence of conjunctivitis in his outpatient practice as a natural background to clinical ophthalmology.

In former days a descriptive classification of conjunctivitis into catarrhal, serous, mucopurulent, pseudomembranous, and membranous satisfied our ophthalmological forefathers, and it was assumed that most cases were of bacterial origin. It cannot be denied that this concept of conjunctivitis is still in the minds of many clinicians. Indeed true bacterial conjunctivitis should not be forgotten, since it can be an alarming condition, as anyone who has seen a case of genuine gonococcal conjunctivitis will agree. Furthermore, there is no knowing nowadays how many cases of bacterial conjunctivitis are cured so rapidly by immediate treatment with antibiotics that they never come to the notice of ophthalmologists.

However, the clinician with recent training, particularly if he is associated with an academic unit, probably thinks more about viruses than bacteria. In the last 40 years or so we have seen how the proportion of cases attributed to virus infection has increased. The change began with the epidemics of shipyard conjunctivitis which occurred during the second world war and was later named epidemic keratoconjunctivitis.[2] Our knowledge progressed with the recognition of the place of the trachoma virus in western urban society.[3,4] Thus adenovirus or TRIC now features prominently in the differential diagnosis in cases of acute follicular conjunctivitis.

The paper in this issue by Professor Darougar and his colleagues now reminds us of another virus which should be considered in this diagnosis. Herpes simplex has been known as a cause of conjunctivitis for some time. Indeed it is mentioned in standard texts as a type of acute follicular conjunctivitis[5] or as a nondescript conjunctivitis,[6] and Jones *et al.*[7] found no less than 20% of their cases of conjunctivitis of viral origin to be due to herpes, but probably to many clinicians, it appeared to be a rarity. All may not agree with the prevalence suggested by the figures published in the present paper, which comes from a highly specialised unit. Indeed in Adler's textbook acute herpetic keratoconjunctivitis is described as rare, with the initial infection frequently accompanied by cold sores on the face.[8] But the message is clear. A casual attitude to conjunctivitis is no longer justified, and the prolonged prescribing of random antibiotics and worse still corticosteroids should no longer be considered acceptable. A proper differential diagnosis of conjunctivitis ought now to be attempted in all cases which do not respond to a short sharp course of antibiotics. A period off all treatment in mild cases is usually justified, though pressure from patients or relatives to do something may sometimes be hard to resist.

References

1 Duke-Elder WS. *System of ophthalmology*. London: Kimpton, 1965: **8** (1).

2 Jawetz E, Kimona SJ, Harma L, Coleman UR, Thygieson P, Nicholas A. Studies on the etiology of epidemic keratoconjunctivitis. *Am J Ophthalmol* 1955; **40:** 200–11.

3 Jones BR, Collier LH, Smith CH. Isolation of virus from inclusion blenorrhoea. *Lancet* 1959; **i:** 902–5.

4 Jones BR. Trachoma and allied infections. *Trans Ophthalmol Soc UK* 1961; **81:** 367–78.

5 Wilson L. *External diseases of the eye*. Hagerstown: Harper and Row, 1979.

6 Miller SJH. *Parsons' diseases of the eye*. Edinburgh: Churchill Livingstone, 1978.

7 Jones BR, Andrews BE, Henderson WG, Schofield PB. The pattern of conjunctivitis at Moorfields during 1956. *Trans Ophthalmol Soc UK* 1957; **77:** 291–305.

8 Scheie H, Albert DM. *Adler's textbook of ophthalmology*. Philadelphia: Saunders, 1969.

British Journal of Ophthalmology, 1985, **69**, 2–6

Epidemiological and clinical features of primary herpes simplex virus ocular infection

S DAROUGAR, M S WISHART, AND N D VISWALINGAM

From the Subdepartment of Virology, Institute of Ophthalmology; and the External Eye Diseases Clinic, Moorfields Eye Hospital, London

SUMMARY The epidemiological and clinical features of primary herpes simplex virus ocular infection in 108 patients were studied. Of these, 69 (64%) were aged 15 or over and only eight (7%) were under the age of 5. Associated upper respiratory tract infection was found in 38 (35%) patients and systemic disorders such as mild malaise, fever, and aching in 34 (31%) patients. Common symptoms were redness, watering, discharge, itching, irritation, and lid swelling, whereas pain, photophobia, lid vesicles and ulcers, and blurred vision were less frequent. The major signs consisted of vesicles and ulcers on the lids, papillary responses which were more severe in the upper lid conjunctiva, follicles which were more common in the lower lid conjunctiva, fine and coarse epithelial punctate keratitis, and subepithelial punctate keratitis. Dendritic ulcers and disciform keratitis were found in 16 (15%) and two (2%) patients respectively. The clinical forms of primary herpes simplex virus ocular infection varied. Moderate or severe disease was observed in 41 (38%) and 16 (15%) patients respectively. In eight (7%) patients the disease presented as an acute follicular conjunctivitis without characteristic lid or corneal lesions. A chronic blepharoconjunctivitis which lasted for months developed in 16 (15%) patients. The epidemiological and clinical features in our patients were compared with features of the disease reported previously.

Herpes simplex virus (HSV) ocular infection is the major cause of corneal blindness in developed countries. In developing countries it is becoming more prevalent, causing more blindness.

HSV ocular infection may present in various clinical forms. Acute blepharoconjunctivitis with or without keratitis, recurrent corneal ulcers, and recurrent stromal keratitis are common forms of the disease.[1] Primary ocular infection may present as an acute follicular conjunctivitis or keratoconjunctivitis with or without characteristic lid or corneal lesions.[2] In recent years we have observed changes in the epidemiological and clinical features of primary HSV ocular infection in patients attending the External Eye Diseases Clinic at Moorfields Eye Hospital. In this report we present the major features of primary HSV ocular infection observed in 108 patients and compare these with the features of the disease reported previously.

Patients and methods

One hundred and eight patients attending the External Eye Diseases Clinic, Moorfields Eye Hospital, during the period 1973-80 were studied. These patients, who had no previous history of HSV ocular infection, presented with acute conjunctivitis associated with either characteristic HSV lid lesions (vesicles and/or ulcers), or typical corneal lesions (ulcers or stromal keratitis) or were HSV isolation positive.

The patients were examined with a Haag-Streit slit-lamp. Symptoms and signs were graded on a 0 to 3 scale (absent, mild, moderate, severe).[3] Swabbings for HSV isolation were taken from the upper and lower lid conjunctivae, placed in a plastic container containing 2SP transport medium[4] with 3% calf serum, and transported in a liquid nitrogen container (−180°C) to the laboratory where they were stored at −70°C. Each specimen was inoculated into two tubes containing HEP-2 cells, incubated at 35°C, and examined regularly for the presence of cytopathic

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effect.[5] Isolates were identified using an immunofluorescent staining technique.

Two blood samples were collected by venepuncture at an interval of two to three weeks. Sera were separated and tested with a complement fixation test for HSV group antibodies.[6]

Results

Age and sex. The patients' ages ranged from 9 months to 66 years with a mean age of 25 years. Of these, 69 (64%) were aged 15 or more, and eight (7%) were under the age of 5 (Fig. 1). The male to female ratio was 1·1 to one.

Seasonal variation. The prevalence of disease was higher in the months of January to June than in July to December (Fig. 2).

Source of infection. The source of infection was identified in 26 (24%) cases. Of these, nine (8%) had been in contact with patients with an active skin HSV infection, and 17 (16%) had HSV lesions on their own lips, nose, or face.

Associated systemic manifestations. In 38 (35%) patients a mild rhinitis and pharyngitis were present at the time of first examination, and 34 of these also complained of mild malaise, fever, and general aching. A mild to moderate ipsilateral preauricular adenitis was found in 65 (60%) cases. This adenitis was more severe in the first week of infection and subsided gradually in five to 10 days. Cervical and submandibular adenitis developed in 18 (17%) and 12 (11%) patients respectively.

Clinical forms. Moderate or severe disease was observed in 41 (38%) and 16 (15%) patients respectively. Blepharoconjunctivitis (conjunctivitis with lid vesicles and/or ulcers) occurred in 100 (93%) patients. Sixteen of these developed dendritic ulcers and two developed disciform keratitis. In eight (7%) cases the disease presented as a follicular conjunctivitis without any typical lid or corneal lesions.

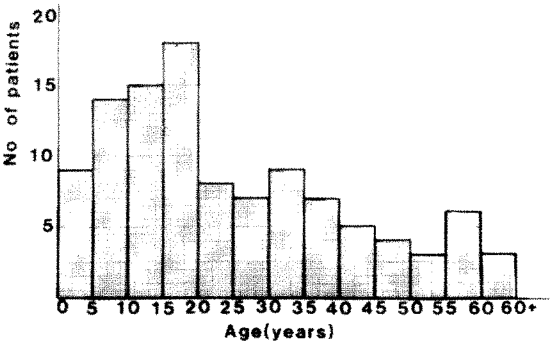

Fig. 1 *Age distribution of 108 cases of primary herpes simplex virus ocular infection.*

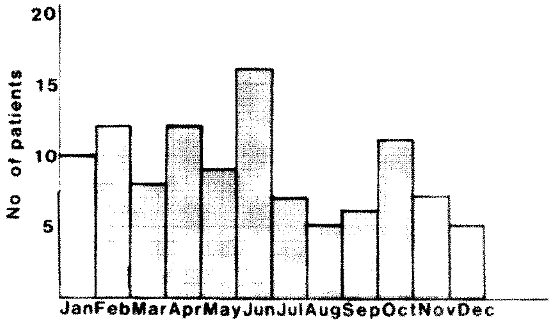

Fig. 2 *Seasonal variation of 108 cases of primary herpes simplex virus ocular infection.*

Ocular infection was unilateral in 88 (81%) patients and bilateral in 20 (19%) patients. The disease was bilateral at onset in 12 patients and became bilateral within one week of onset in eight patients.

Course of infection. Mild to moderate infections generally lasted for two to three weeks. In severe disease the acute phase of the infection lasted three to five weeks. In 16 (15%) patients a chronic blepharoconjunctivitis developed which lasted for months.

Symptoms. The common symptoms were redness, watering, discharge, itching, irritation, and lid swelling, whereas pain, photophobia, lid vesicles and/or

Table 1 *Prevalence and severity of symptoms in 108 cases of primary HSV ocular infection*

Symptoms	*Severity*			
	Absent	*Mild*	*Moderate*	*Severe*
Redness	18	53	34	3
Watering	25	48	30	5
Discharge	27	47	30	4
Irritation and itching	35	58	14	1
Swelling of lids	30	42	26	10
Lid vesicles and/or ulcers	59	30	19	0
Photophobia	57	39	10	2
Blurred vision	74	30	2	2
Pain	80	26	2	0

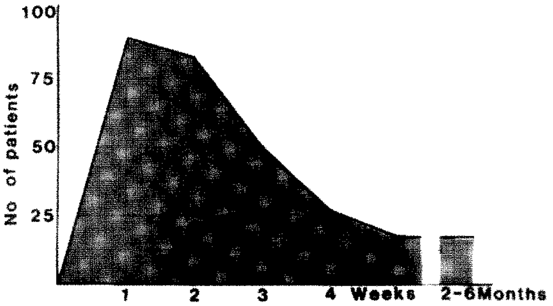

Fig. 3 *Prevalence and duration of symptoms in 108 patients with primary herpes simplex virus ocular infection.*

Table 2 *Prevalence and severity of signs in 108 cases of primary HSV ocular infection*

Area	*Signs*	*Severity*			
		Absent	*Mild*	*Moderate*	*Severe*
Lids	Vesicles and/or ulcers	8	59	31	10
Bulbar conjunctiva	Hyperaemia	22	53	30	3
	Chemosis	76	24	8	0
	Ecchymosis	93	14	1	0
Palpebral conjunctiva	Hyperaemia	9	43	45	11
	Oedema	10	47	44	7
	Papillae	2	15	55	36
	Follicles	7	41	51	9
	Pseudomembrane	104	2	2	0
Cornea	Epithelial punctate keratitis	72	27	5	4
	Subepithelial punctate keratitis	87	16	4	1
	Erosion	101	6	0	1
	Dendritic ulcer	92	12	4	0
	Disciform keratitis	106	1	1	0

ulcers and blurred vision were less frequent (Table 1). Symptoms were most prevalent in the first two weeks but subsided during the next two to three weeks (Fig. 3). However, in 16 (15%) patients mild redness, irritation, discomfort, watering, discharge, and photophobia continued for several months.

Signs. The major signs observed were associated with the lids, conjunctiva, or cornea (Table 2).

On the *lids* vesicles and/or ulcers occurred in 100 (93%) patients (Fig. 4). These were moderate or severe in 41 patients (Table 2). Vesicles were common in the first week of infection, whereas ulcers occurred more commonly in the second week and usually lasted for two to three weeks. However, in seven cases ulcers persisted for four to five weeks. In 16 (15%) patients a chronic blepharitis consisting of mild to moderate lid margin erythema, scales, and meibomitis developed. This chronic blepharitis lasted for months.

The *bulbar conjunctiva* showed mild to moderate hyperaemia in 83 (77%) and severe hyperaemia in three (3%) patients. Mild to moderate chemosis was observed in 32 (30%) patients. Ecchymosis was observed in 15 (14%) patients (Table 2). In the *palpebral conjunctiva* moderate to severe hyperaemia and oedema were observed in 56 (52%) and 51 (47%) patients respectively. Papillae were found in all except two patients (Table 2). The papillary response was moderate or severe in 91 (84%) patients. It was more severe in the upper lid conjunctiva than in the lower and usually lasted for four to eight weeks. In 35 (32%) patients a mild to moderate papillary response persisted for six months or more (Fig. 5). Follicular hypertrophy was found in 101 (94%) patients and was moderate to severe in 60 (56%) patients (Table 2). The follicles were small, discrete, and found mainly in the lower lid conjunctiva. In most cases they persisted for four to eight weeks (Fig. 6). However, in 26 (24%) patients small follicles were still present four to six months after the onset of infection (Table 2). In four (4%) patients a mild to moderate pseudomembrane was present.

Corneal signs comprising punctate keratitis, erosion, dendritic ulcer, or stromal keratitis were

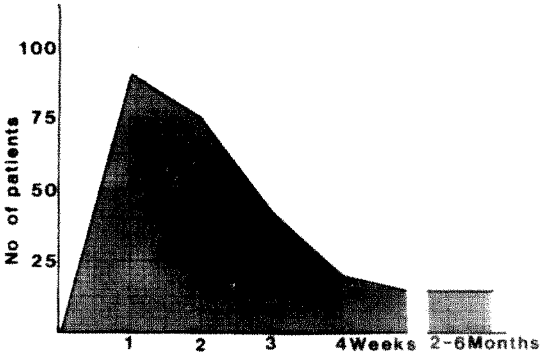

Fig. 4 *Prevalence and duration of lid signs in 108 patients with primary herpes simplex virus ocular infection.*

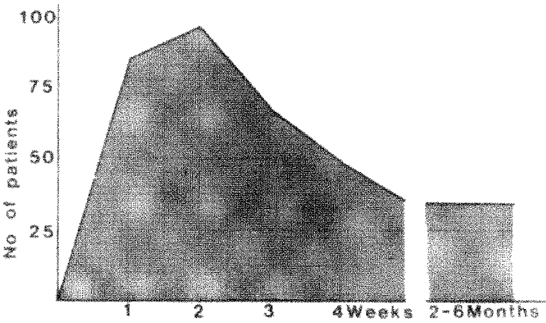

Fig. 5 *Prevalence and duration of the conjunctival papillary response in 108 patients with primary herpes simplex virus ocular infection.*

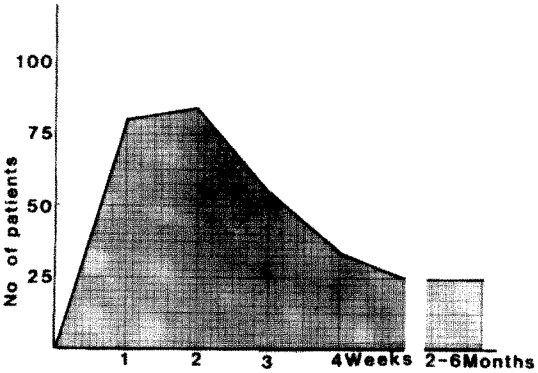

Fig. 6 *Prevalence and duration of the conjunctival follicular response in 108 patients with primary herpes simplex virus ocular infection.*

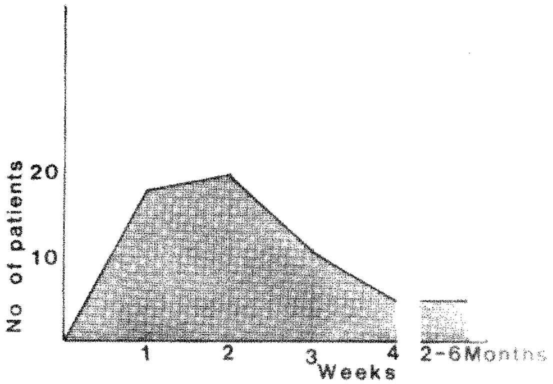

Fig. 7 *Prevalence and duration of epithelial punctate keratitis in 108 patients with primary herpes simplex virus ocular infection.*

found in 36 (33%) patients. A mild to moderate fine epithelial punctate keratitis (EPK)[7] appeared during the first week of the infection. In most cases this disappeared within three weeks (Fig. 7). In 21 (19%) patients EPK was followed by subepithelial punctate keratitis (SEPK)[7] (Table 2). SEPK appeared in the first three weeks of infection and was more prominent during the third and fourth weeks (Fig. 8). In six cases SEPK lasted for several months. Small corneal erosions, which stained with fluorescein, were detected in seven (6%) patients. Dendritic ulcers were detected in 16 (15%) patients. These ulcers developed between days 5 and 10 and lasted for one to two weeks. Diffuse stromal keratitis, presenting as disciform keratitis, developed in two (2%) patients (Table 2).

Virus isolation. Conjunctival specimens were collected from 69 patients, and HSV was isolated from 42 (61%) patients. Fifty-three specimens were collected during the first week of infection of which 34 (64%) were positive. Eight out of 16 specimens (50%) collected during the second week were positive.

Antibodies. Forty paired sera were tested for the presence of group-specific HSV antibodies. Fourfold or higher rises in titre were detected in nine out of 40 (23%) of these.

Discussion

Primary HSV ocular infection can constitute up to 23% of all cases of acute conjunctivitis presenting at ophthalmic outpatient clinics.[8,9] The true prevalence may be much higher, because patients with mild forms of conjunctivitis with a few lid lesions, and those with acute conjunctivitis without characteristic lid or corneal lesions, generally attend their family doctor. Hence, these conditions may remain largely unrecognised, and treated unnecessarily with antibiotics, or be exposed to the hazards of steroid treatment.[8]

In this series of patients the epidemiological and clinical features of primary HSV ocular infection differed from previous reports. It has been reported that primary ocular HSV infection presents predominantly in two age groups with equal prevalence.[8] The first consists of children who have been kissed by their infected parents, and the second consists of young adults who have been kissed by their infected partners. In London the age distribution of ocular HSV infection appears to have changed. In a previous study[10] five out of 17 patients (29%) were under the age of 5, whereas in the present series only eight out of 108 patients (7%) were under 5. In contrast the proportion of cases in adolescents and young adults has increased from 41% (seven out of 17)[10] to 64% (69 out of 108) in the present series. It has been reported that the prevalence of antibodies against HSV type 1 in young adults is declining,[11] indicating that infections in childhood are less common. The decrease which we have observed in the proportion of children with primary HSV ocular infection may be a reflection of this decline. The increased pro-

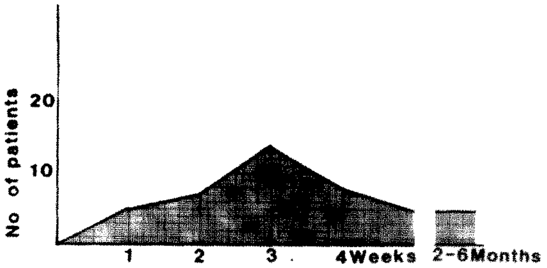

Fig. 8 *Prevalence and duration of subepithelial punctate keratitis in 108 patients with primary herpes simplex virus ocular infection.*

portion of cases of primary HSV ocular infection in young adults may be the result of very low rates of infection in childhood.

We observed moderate and severe conjunctivitis and blepharitis in 84% and 38% of patients respectively. In previous studies of primary HSV ocular infection in London[8,10] and elsewhere[1,12] there were no records of the severity of disease to compare with our findings. However, considering the general statements in these reports and our observations in the External Eye Diseases Clinic at Moorfields Eye Hospital during the past two decades (unpublished data) we believe that primary HSV ocular infection is presenting in more severe forms. This increase in the severity of disease in our patients may be also due to a decrease in the prevalence of HSV infection during childhood. Studies have shown that HSV ocular infection is generaly milder in those who have been previously exposed to HSV in the eye or elsewhere.[8]

In 7% of our patients the disease presented as an acute follicular conjunctivitis without typical lid or corneal lesions. Sporadic cases of HSV follicular conjunctivitis have been reported previously.[2,10,12,13] The largest number of such cases has been found in London, and most of these patients were between 20 and 35 years old.[2] The clinical features, comprising moderate to severe papillary and follicular responses with or without EPK or SEPK, are similar to those of adenovirus and the early stages of chlamydial ocular infections. It has been reported that HSV may be responsible for up to 21% of cases of acute conjunctivitis in London.[9] However, in the absence of routine laboratory investigations for HSV in cases of acute conjunctivitis or keratoconjunctivitis such cases cannot be correctly diagnosed and treated.

In this study dendritic ulcers and disciform keratitis were found in 16 (15%) and two (2%) patients respectively. Patterson and Jones[10] reported the development of dendritic ulcers and disciform keratitis in one out of 17 patients with primary HSV ocular infection. Our study confirms the observation that dendritic ulcers and disciform keratitis occur in primary as well as recurrent HSV ocular infection.

In the present series 16 (15%) patients developed a chronic blepharoconjunctivitis with mild symptoms and mild to moderate signs consisting of lid margin erythema, scales, meibomitis, papillary, and follicular responses. This lasted for several months. In these patients laboratory investigations showed no evidence of bacterial or allergic aetiology. These findings suggest that HSV may be a cause of chronic blepharitis and blepharoconjunctivitis.

The authors are grateful to colleagues at Moorfields Eye Hospital for referring the patients and to Miss U Thaker for assistance in laboratory work. The study was supported by a grant from the Department of Health and Social Security through Moorfields Eye Hospital.

References

1 Darougar S, Treharne JD, and Monnickendam MA. Herpes simplex virus infections of the eye. In: Waterson, AP ed. *Recent advances in clinical virology*. London, Churchill Livingstone, 1980; 131–46.

2 Darougar S, Hunter PA, Viswalingam ND, Gibson JA, Jones BR. Acute follicular conjunctivitis and keratoconjunctivitis due to herpes simplex virus in London. *Br J Ophthalmol* 1978; **62:** 843–9.

3 Darougar S, Viswalingam ND, Treharne JD, Kinnison JR, Jones BR. Treatment of TRIC infection of the eye with rifampicin or chloramphenicol. *Br J Ophthalmol* 1977; **61:** 255–9.

4 Gordon FB, Harper JA, Quan AL, Treharne JD, Dwyer RStC, Garland JA. Detection of Chlamydia (Bedsonia) in certain infections of man. I. Laboratory procedures: comparison of yolk sac and cell culture for detection and isolation. *J Infect Dis* 1969; **120:** 451–62.

5 McSwiggan DA, Darougar S, Rahman AFNS, Gibson JA. Comparison of the sensitivity of human embryo kidney cells, HeLa cells and WI38 cells for the primary isolation of viruses from the eye. *J Clin Pathol* 1975; **28:** 410–13.

6 Bradstreet CM, Taylor CED. Technique of complement-fixation test applicable to the diagnosis of virus diseases. *Monthly Bulletin of the Ministry of Health and Public Health Laboratory Service* 1962; **21:** 96–104.

7 Jones BR. Adenovirus infection of the eye in London. *Trans Ophthalmol Soc UK* 1962; **82:** 621–44.

8 Jones BR. The management of ocular herpes. *Trans Ophthalmol Soc UK* 1959; **79:** 425–37.

9 Wishart PK, James C, Wishart MS, Darougar S. Prevalence of acute conjunctivitis caused by chlamydia, adenovirus and herpes simplex virus in an ophthalmic casualty department. *Br J Ophthalmol* 1984; **68:** 653–5.

10 Patterson A, Jones BR. The management of ocular herpes. *Trans Ophthalmol Soc UK* 1967; **87:** 59–84.

11 Anonymous. Herpes simplex—changing patterns. (Editorial). *Lancet* 1981; **ii:** 1025–6.

12 O'Day D, Jones BR. Herpes simplex keratitis. In: Duane, TD ed. *Clinical ophthalmology* Hagerstown: Harper and Rowe, 1980, **4:** 11–26.

13 Maumenee AE, Hayes GS, Hartman TZ. Isolation and identification of the causative agent in epidemic keratoconjunctivitis (superficial punctate keratitis) and herpetic keratoconjunctivitis. *Am J Ophthalmol* 1945; **28:** 823–39.

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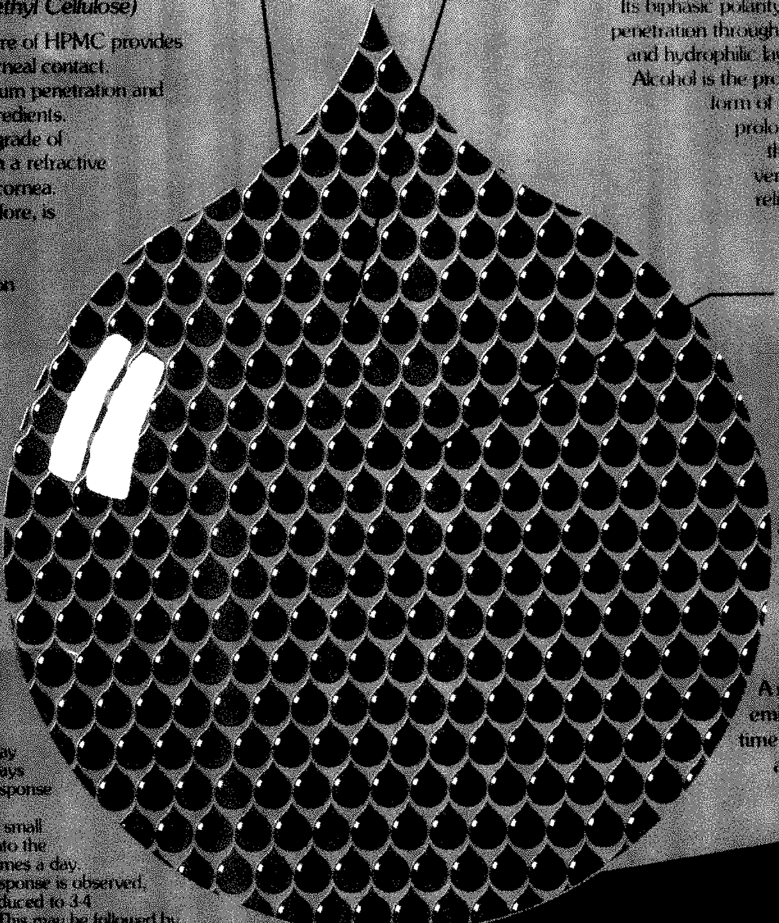

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Histiocytosis X: an ophthalmological review

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SUMMARY Of 76 children with histiocytosis X 18 had orbital involvement, and four developed additional neuro-ophthalmic complications. No instance of intraocular involvement was detected. Among those patients with ophthalmic involvement the main problems were bilateral or unilateral proptosis, ptosis, papilloedema, optic atrophy, and seventh nerve palsy. Only one patient developed a severe visual defect. Management of the ophthalmological complications depends not only on the extent of the orbital disease but also on the degree of systemic involvement. Overall management by a paediatric oncologist is mandatory.

Histiocytosis X is an uncommon multisystem disorder of unknown aetiology, which is characterised by accumulation of histiocytes in various tissues and which runs a variable clinical course. It is predominantly a disease of childhood but is occasionally seen in adults.[1] It has an affinity for the orbit. Ophthalmologists may be asked to see children with disseminated disease who develop proptosis during the course of their illness, but isolated orbital involvement is sometimes the presenting feature.

Histiocytosis X was a term first proposed by Lichtenstein in 1952[2] to cover three related disorders, eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease, which he believed were different clinical expressions of a single nosological entity. 'Eosinophilic granuloma' was first coined by Lichtenstein and Jaffe[3] to describe a single histiocytic lesion in bone, but it was later used to describe a condition where the histiocytic lesions, which may be multiple, were confined to bone. The original description of Hand-Schüller-Christian disease was of the triad of exophthalmos, bony defects of the skull, and diabetes insipidus. Strictly speaking this exact combination is rare,[1 4 5] but the eponym is sometimes used to describe the chronic disseminated form of histiocytosis X involving both bone and soft tissues. Letterer-Siwe disease usually occurs in infancy with widespread soft tissue and visceral involvement with or without bony lesions, and it has a subacute, and sometimes fatal, course.

Newton and Hamoudi[6] have correlated histological appearance with clinical prognosis and proposed a histopathological classification of histiocytosis X, but this has not gained widespread acceptance.[7] As it is not possible to distinguish these three groups on histopathological appearance of involved tissues, and as there is considerable clinical overlap between the three conditions,[8] it is now generally agreed that the generic term histiocytosis X should be used in preference to the eponymous subclassification.

We present here our experience with histiocytosis X and discuss the clinical features and management of the ophthalmological complications of this condition.

Material and methods

The case records of all children with histiocytosis X seen at the Hospital for Sick Children over a 26-year period from 1957 were reviewed for evidence of ocular or orbital involvement with histiocytosis X. Owing partly to changes in referral patterns half the patients had presented in the last six years.

Results

The records of 76 patients were examined. The age range was from birth to 12 years, and 30% were under the age of one year at presentation (Fig. 1). The majority of patients (39) had involvement of bone and soft tissue, while 26 patients had disease confined to bone, and in 11 patients there was soft tissue involvement only. There were no cases of

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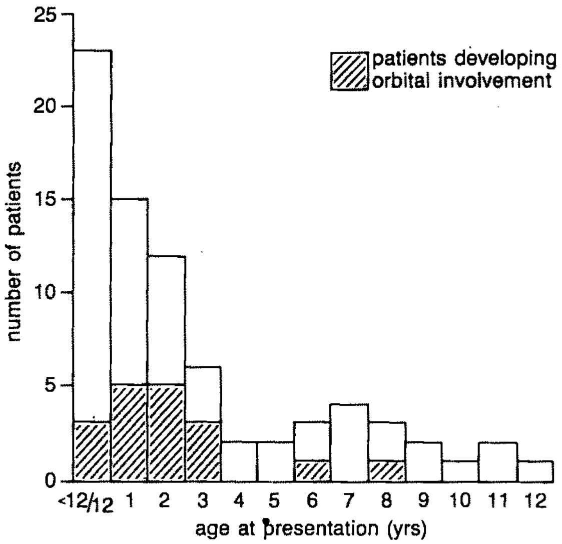

Fig. 1 *Histiocytosis X. Age at presentation and orbital involvement.*

orbital involvement in this latter group (Table 1). Three patients had diabetes insipidus at presentation, and a further nine patients developed it at a later stage. Classical Hand-Schüller-Christian disease, with bilateral proptosis, diabetes insipidus, and bony defects of the skull, was seen in only two patients.

Eighteen patients developed orbital involvement with histiocytosis X, half of these from the time of presentation. In 16 the diagnosis of histiocytosis X was confirmed by histopathology. Each of the two patients who did not have biopsies showed the typical clinical and radiological features of chronic disseminated histiocytosis X. Eleven patients developed unilateral proptosis, five developed bilateral proptosis, and two presented with unilateral ptosis in association with a localised orbital lytic lesion. Of particular interest are three patients who presented with isolated orbital involvement with histiocytosis X. Two of these patients showed spontaneous resolution of their disease after biopsy, and in the third case (case 2) the disease ran an unusually locally aggressive course. None of these three cases has yet shown any additional manifestations of histiocytosis X, although the follow-up period is short (2½–3½ years).

Table 1 *Orbital involvement in Histiocytosis X*

	Patients with general involvement	*Patients with orbital involvement*
Group 1 Bone involvement only	26	6
Group 2 Soft tissue involvement only	11	0
Group 3 Bone and soft tissue involvement	39	12
Total	76	18

None of our patients had evidence of intraocular involvement with histiocytosis X, but the eyes of infants with acute disseminated disease were not routinely examined if they were asymptomatic, and no eyes were examined at necropsy. Two patients with disseminated histiocytosis X and bilateral proptosis developed bilateral papilloedema. In one (case 3) there was cerebral involvement with histiocytosis X and raised intracranial pressure. Bilateral optic atrophy later ensued with severe loss of vision. In the second case necropsy showed extensive bilateral orbital involvement with histiocytosis X and gross cerebral oedema but no evidence of cerebral infiltration with histiocytes. One patient developed unilateral proptosis and optic disc swelling during his illness. The disc oedema, thought to be due to localised optic nerve involvement with histiocytosis X, resolved without sequelae after treatment with chemotherapy. One other patient developed a transient seventh nerve palsy. Only one patient in the series was left with a significant degree of visual handicap.

The following cases illustrate the variable clinical course of this condition.

ILLUSTRATIVE CASES

Case 1. This 15-month-old boy presented in January 1980 with a left ptosis and swelling of the left upper lid. His general health was otherwise good. Examination revealed a left ptosis and a palpable mass in the upper part of the left orbit (Fig. 2A). Eye examination was otherwise normal. *X*-rays of the left orbit showed an area of bone destruction at the superolateral aspect of the left orbit (Figs. 2B, C), and orbital CT scan showed a small extraconal mass at the lateral side of the left orbit. General examination, liver scan, bone scan, skeletal survey, bone marrow examination, and urinary osmolality were all normal. Biopsy of the lesion showed the typical histological appearance of histiocytosis X. No treatment was given, and the ptosis and orbital mass resolved over the next five months (Fig. 2D). *X*-ray examination at this time showed healing of the orbital lesion. He has remained well with no recurrence of histiocytosis X.

Case 2. This 8-year-old boy presented in March 1980 with a history of a left periorbital swelling present for two months. He had been born in England of Jamaican parents, and apart from frequent upper respiratory tract infections in childhood had been generally well. On examination the vision was 6/6 RE and 6/9 LE. A rubbery mass was palpable around the upper and lower orbital margins and extending over the lateral wall and down over the

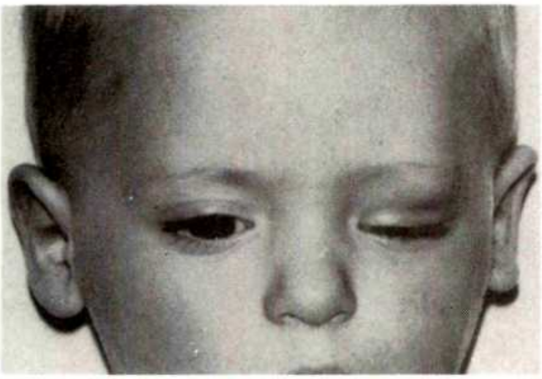

Fig. 2A

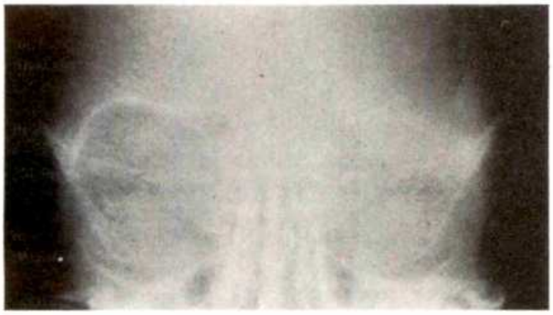

Fig. 2B

Fig. 2 *Case 1.* A: *Left ptosis associated with orbital histiocytosis X.* B *and* C: *anteroposterior and lateral x-rays showing lytic lesion of left orbit with surrounding area of bony sclerosis.* D: *after resolution.*

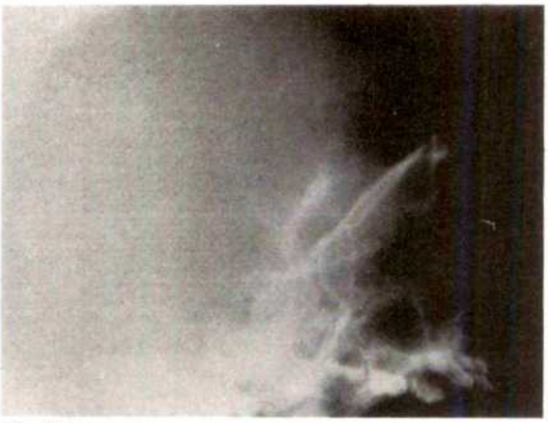

Fig. 2C

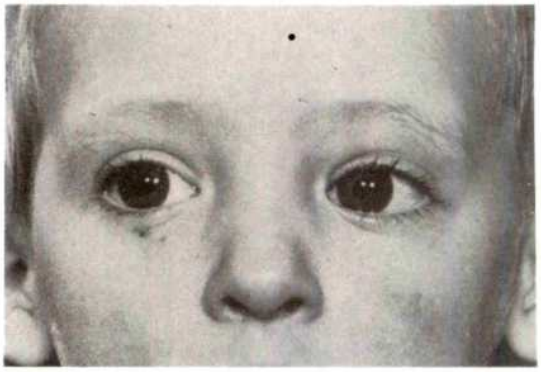

Fig. 2D

zygoma. There was 6 mm of left axial proptosis (Fig. 3A), but eye movements, pupil reactions, and fundus examination were normal. *X*-rays of the orbit showed a lytic lesion of the lateral wall, and CT scan showed a left orbital mass (Fig. 3B). A biopsy of the orbital mass showed the typical appearance of histiocytosis X. General examination, chest *x*-ray, skeletal survey, bone marrow, and urinary osmolalities were all normal.

Because there was no shrinkage after excision biopsy and because of the cosmetic appearance, the left orbit was treated in July 1980 with radiotherapy (1000 cgray). Initially there was a favourable response, but by the end of 1981 the mass had extended to involve the temporal fossa, and a large tumour mass was evident on the surface of the skin (Fig. 3C). The degree of proptosis and visual acuity was unchanged. In February 1982 the main part of the lesion was excised, and the underlying abnormal tissue curetted from the bone leaving a large defect in the lateral orbital wall and over the maxilla. Histology of the excised tissue again showed histiocytosis X. Depo-Medrone 80 mg (methyleprednisolone acetate), and Solu-medrone 100 mg (methylprednisolone sodium succinate) were injected into the residual tumour on four occasions over the next six months, and the tumour became smaller. When the patient was last seen in December 1982 the vision was 6/6 RE and 6/9 LE. There was 6 mm of left axial proptosis (Fig. 3D), but eye examination was otherwise normal. He has developed no further manifestations of histiocytosis X.

Case 3. This 2½-year-old Pakistani girl presented in July 1978 with fever and bilateral proptosis. There was bilateral axial proptosis, but eye examination was otherwise normal. There was a palpable mass on the vertex of the skull and over the left zygoma, an eczematous rash on the scalp, and a palpable liver and spleen. Skull *x*-ray showed several lytic lesions, and biopsy of one of the skull lesions showed histiocytosis X (Fig. 4). Chest *x*-ray and bone marrow examination were normal. Treatment was started with prednisolone and vinblastine, and when reviewed three months later she appeared to be

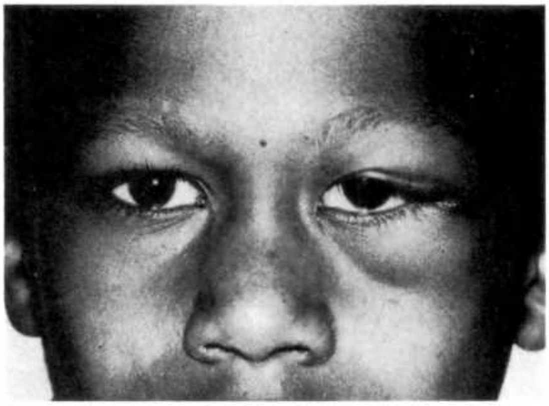

Fig. 3A

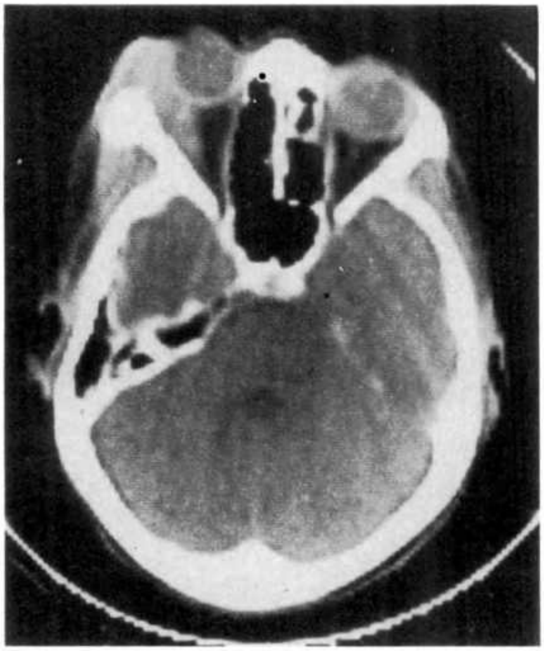

Fig. 3B

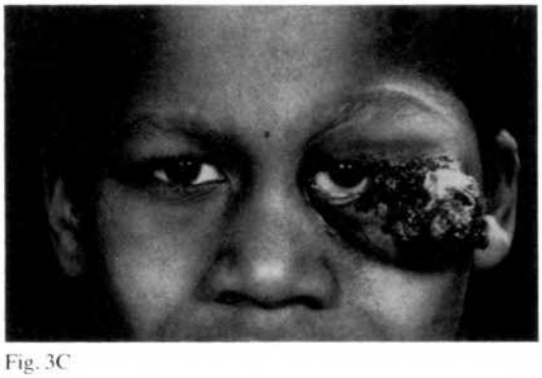

Fig. 3C

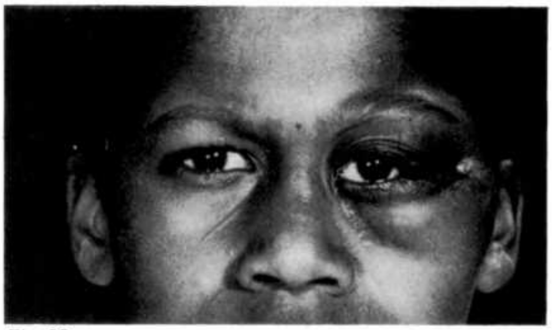

Fig. 3D

Fig. 3 *Case 2. Histiocytosis X of the left orbit.* A: *At presentation.* B: *CT scan showing left orbital mass.* C: *Recurrence after radiotherapy.* D: *At last follow-up visit.*

responding to treatment, and the proptosis was less marked.

Chemotherapy was stopped in March 1979, but this was soon followed by worsening of her bilateral proptosis and the appearance of new lesions of the skull and zygoma. Her pupil reactions and fundus examination were normal. CT scan showed bilateral soft tissue masses in both orbits with bilateral invasion of the middle cranial fossa. Chemotherapy was restarted, and both orbits, pituitary areas, and middle cranial fossa were treated with radiotherapy (1500 cgray). She returned to Pakistan, where treatment was continued with prednisolone, vinblastine, and, later, cyclophosphamide.

In May 1981 she returned to London for review. She had been drowsy and vomiting for one month. On examination the proptosis was more marked. There was a mass in the left upper lid, a left relative afferent pupil defect, and bilateral disc oedema. CT scan (Fig. 7) showed increased size of the orbital masses, dilated third and fourth ventricles, and oedema of both temporal lobes. She initially improved on dexamethasone, but when she was re-examined six months later there was again a left afferent pupil defect, but now there was bilateral optic atrophy thought to be secondary to raised intracranial pressure. CT scan showed bilateral orbital masses and low attention in both temporal lobes and posterior fossa. A ventriculoperitoneal shunt was inserted and a brain biopsy taken, which confirmed cerebral involvement with histiocytosis X. Postoperatively the vision deteriorated. There was no pupillary response to light, and there was bilateral optic atrophy. Electrodiagnostic tests showed a normal ERG but absent visual evoked response from each eye. The patient returned to Pakistan and we have no further follow-up.

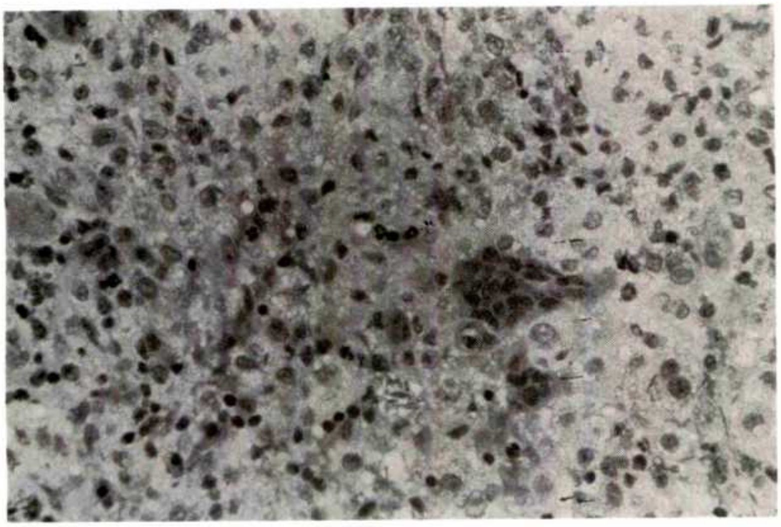

Fig. 4 *Case 3. Skull biopsy specimen. Light microscopy of the biopsy revealed similar changes in all three illustrative cases. The infiltrate comprised a mixture of mononuclear histiocytes with indented nuclei and smaller numbers of multinucleate giant cells, eosinophils, neutrophils, and lymphocytes.*

Discussion

Histiocytosis X is an uncommon cause of orbital tumour and is not mentioned in several series of paediatric orbital tumours.[9-12] Henderson[13] found that histiocytosis X accounted for just 1% of a total of 764 orbital tumours seen in both children and adults at the Mayo Clinic over a 26-year period. All but one of these cases were in children under the age of two years. In a large series of paediatric orbital tumours Crawford[14] found histiocytosis X represented 7% of 257 cases of proptosis seen in children under the age of 15 presenting at a large children's hospital. The variation in these figures probably reflects the referral pattern of the different centres. Ophthalmologists who work in hospitals with a regional paediatric oncology unit are more likely to see orbital histiocytosis X than, for example, those working in eye hospitals or neurosurgical units.

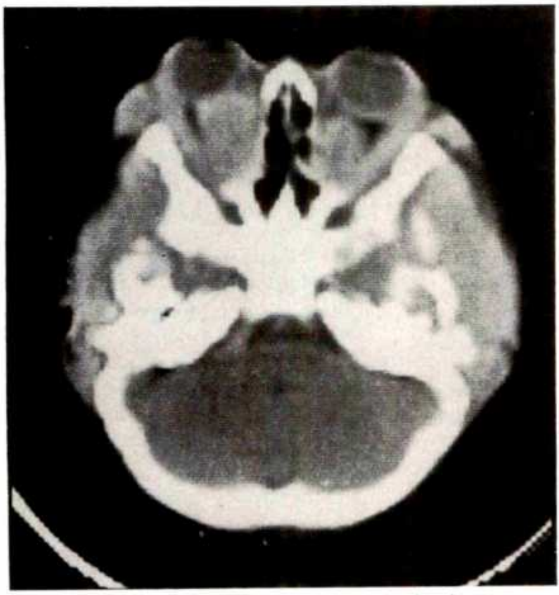

Fig. 5 *Case 3. CT Scan showing bilateral orbital mass.*

In patients with histiocytosis X orbital involvement is, however, common, and with some exceptions[15,16] is usually seen in the chronic form of the disease[5] especially 'Eosinophilic granuloma'.[17-24] The overall incidence of orbital involvement in larger series of patients with histiocytosis X is about 20%,[5,25] but only half of these patients developed proptosis.[1,4,26] In our series 23% of patients had clinical signs of orbital involvement, and most had proptosis. There may be radiological evidence of orbital involvement without any accompanying clinical signs, but proptosis is almost invariably associated with a lytic lesion of the orbital wall.[15] In our study there were no cases of orbital involvement in patients whose disease was confined to the soft tissue (Table 1), suggesting that in histiocytosis X the orbital lesion usually arises in bone.

Intraocular involvement by histiocytosis X is rare. It is usually seen in infants with the subacute disseminated form and consists of infiltration of intraocular structures, especially the uveal tract, with histiocytes.[27-34] This may be an incidental finding at necropsy,[29,31,33] but some patients will present with ocular abnormalities during their acute illness.[27,28,30,32-34] Mozziconacci *et al.*[27] reported on a 2-year-old girl with Letterer-Siwe disease who first developed choroidal infiltrates and later a total retinal detachment. The eye was subsequently enucleated, and histological examination showed infiltration of the choroid, retina, and vitreous with histiocytes. Rupp and Holloman[30] reported on a 3-month-old child with histiocytosis X who developed uveitis, iris infiltration, and spontaneous hyphaema during the course of her illness. Necropsy of the eye showed histiocytic infiltration of the uveal tract. Secondary open-angle glaucoma,[28] bilateral perforating corneal ulcers,[29] and posterior scleritis[32] have also been reported.

In contrast, orbital involvement is rare in the acute disseminated form of histiocytosis X[5] as confirmed in this study. It is usually seen in patients with the chronic disseminated form. Optic neuropathy and cranial nerve palsies are rare[17 24] as the orbital mass is usually extraconal, and destruction of the orbital walls may result in orbital decompression. Beller and Kornbleuth,[17] however, reported a 14-year-old boy who developed optic neuropathy and third, fourth, and sixth cranial nerve palsies. The optic nerve and chiasm may become involved by intracranial histiocytosis X, which has a predilection for the pituitary gland.[35] Papilloedema and secondary optic atrophy may result from raised intracranial pressure secondary to intracranial involvement with histiocytosis X.[36] Although orbital and pituitary involvement with histiocytosis X was commonly seen in our series, only four patients developed neuro-ophthalmic complications.

The diagnosis of histiocytosis X is ultimately confirmed by histopathological examination of biopsy specimens of involved tissues. In children with orbital involvement as part of systemic disease it is usually easier to take a biopsy specimen from another site such as the scalp, or a peripheral bony lesion. In isolated orbital involvement the diagnosis should be suspected when a child presents with periorbital swelling, ptosis, or proptosis, and there is evidence of a lytic lesion on *x*-ray, with or without a narrow zone of sclerosis (Fig. 2B). The radiological appearances are, however, variable[37] and may resemble Ewing's sarcoma, oesteomyelitis, metastatic tumour—especially neuroblastoma or lymphoblastic leukaemia—or even fibrous dysplasia. The diagnosis may, therefore, be in doubt until histopathology is available. In children with isolated orbital involvement it is usually possible to take a biopsy specimen from the involved orbital bone without having to enter the orbit. The bone will be found to be infiltrated by soft yellow-brown material which is easily curetted. Orbital histiocytosis X must be differentiated from other histocytic disorders which may involve the orbit, such as sinus histiocytosis,[38 39] and juvenile xanthogranuloma (JXG). These conditions, however, usually remain confined to the orbital soft tissues and do not involve bone, although JXG may rarely result in orbital bony destruction.[40 41] If there are no other systemic features, it may be difficult to distinguish between orbital histiocytosis X and JXG clinically, but light and electron microscopy of a biopsy specimen are diagnostic.

Children whose disease is confined to a single system such as bone or skin have a good prognosis, though there may be a later recurrence in about one-third of cases.[8] In patients with a single bony lesion biopsy and curettage may be followed by spontaneous resolution, as occurred in two of our patients. However, if there is marked proptosis, or a cosmetically unacceptable lesion of the orbital wall, or evidence of optic nerve involvement, a short course of systemic steroids or radiotherapy may be used in an attempt to induce remission. A radiation dose of 500–600 cgray is usually sufficient and a total dose of not more than 1000 cgray is recommended.[42] There is no evidence that lesions which do not respond to 1000 cgray will respond to a higher dose, and because of the fear of radiation induced malignancy later in life this dose should be exceeded only in exceptional circumstances. An alternative approach to disfiguring lesions of the orbital wall is to remove the main mass of the lesion surgically, with curettage of the underlying bone. Intralesional steroids as used in Case 2 may also be tried.[43] The relative infrequency of optic nerve compression and the good response to radiotherapy or chemotherapy means that surgical exploration of the orbit is rarely necessary. In patients with disseminated histiocytosis X, orbital disease, causing proptosis, will generally respond to systemic chemotherapy, though local radiotherapy may be used in addition if there is progressive proptosis or optic nerve involvement. In view of the tendency to spontaneous regression, in both single system disease (as illustrated in case 1) and in multisystem[44] disease, we recommend a conservative therapeutic approach, including an initial period of observation, without specific therapy.

The most frequently used systemic agents are prednisone, vincristine, or vinblastine, and the epipodophyllotoxin VP16. The response rate to multidrug regimens is no greater than to single or double agent therapy, and the complication rate is higher.[8] Therefore, we commence chemotherapy, if it is needed, with prednisone alone, adding vincristine where the response to steroids is inadequate and using VP16 in resistant disease.

Recent investigations have shown a subtle immunological defect in patients with histiocytosis X. Osband *et al.*[45] found a relative suppressor cell deficiency in the peripheral blood mononuclear cells of patients with multiple organ involvement. This finding has been confirmed in a separate group of children (including one of the patients reported here) with histiocytosis X limited to the skeletal system.[46] Though immunohistochemical studies confirm that the histiocytosis X disease process is characterised by abnormal accumulation of histiocytes, including Langerhans cells,[47] it is not yet clear whether suppressor cell deficiency is the cause of the disordered histiocytic proliferation or an unrelated 'secondary' effect. However, the presence of the same immunological abnormality in patients with both single system and multisystem disease adds weight to the clinical[8] and histopathological[7] evidence supporting Lichtenstein's 'unifying' concept of the histiocytosis X disorders.[2]

After demonstrating that the suppressor cell deficiency could be corrected in vitro by 'thymosin' (a crude extract of calf thymus), the Boston group administered this material intramuscularly to a group of children with newly diagnosed histiocytosis X.[45] The overall 'response rate' was 60%, a figure comparable with that achieved with chemotherapy. In London we have studied the effects of synthetic analogues (TP1 and TP5) believed to represent the active moiety of 'thymosin'. Though we confirmed that the reduced suppressor: helper lymphocyte ratio was corrected by TP1 or TP5 in the majority of patients, there was no clinical response to these preparations in five patients.[46] Because of the tendency to spontaneous remission in histiocytosis X[44] it is essential that future studies of novel forms of therapy, such as thymic hormones, include controlled, randomised trials.

The prognosis in histiocytosis X depends upon several factors: the age of onset, the extent of disease, and the presence or absence of organ failure. The prognosis is worse in infants, and death is rare in children who present after the age of 3 years.[4 48] Single system disease is associated with a good prognosis. Children with multisystem disease may die because of failure of key organs such as bone marrow, liver, and lungs. Though there is a significant morbidity in survivors, who may develop growth failure, diabetes insipidus, or respiratory problems, long-term visual problems are rare.

New cases of histiocytosis X presenting to the ophthalmologist are best managed in collaboration with a paediatric oncologist. Advice from other specialists such as ENT and orthopaedic surgeons may be needed for specific problems. Even if there is no clinical evidence of systemic involvement, chest *x*-ray, skeletal survey, bone marrow examination, lung and liver function tests, and early morning urine specific gravity are needed to assess the extent of the disease and will determine the appropriate treatment.

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References

1 Enriquez P, Dahlin DC, Hayles AB, Henderson ED. Histiocytosis X: A clinical study. *Mayo Clin Proc* 1967; **42:** 88–99.
2 Lichtenstein L. Histiocytosis X. Integration of eosinophilic granuloma of bone, "Letterer-Siwe disease" and "Schüller-Christian disease" as related manifestations of a single nosological entity. *Arch Pathol* 1953; **56:** 84–102.
3 Lichtenstein L, Jaffe HL. Eosinophilic granuloma of bone with report of a case. *Am J Pathol* 1940; **16:** 595–604.
4 Lucaya JL. Histiocytosis X. *Am J Dis Child* 1971; **121:** 289–95.
5 Oberman HA. Idiopathic histiocytosis: a correlative review of eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease. *J Pediatr Ophthalmol* 1968; **5:** 86–92.
6 Newton WA, Hamoudi AB. Histiocytosis: a histological classification with clinical correlation. In: Rosenberg HS, Bolande RP, eds. *Perspectives in pediatric pathology.* Chicago, Illinois: Year Book Publishers, 1973; **1:** 251–81.
7 Risdall RJ, Dehner LP, Duray P, Kobrinsky N, Robison L, Nesbit Jr ME. Histiocytosis X (Langerhans' cell histocytosis): prognostic role of histopathology. *Arch Pathol Lab Med* 1983; **107:** 59–63.
8 Pritchard J. Histiocytosis X: natural history and management in childhood. *Clin Exp Dermatol* 1979; **4:** 421–33.
9 Youseffi B. Orbital tumours in children: a clinical study of 62 cases. *J Pediatr Ophthalmol* 1969; **6:** 177–81.
10 Porterfield JF. Orbital tumours in children: a report on 214 cases. *Int Ophthalmol Clin* 1962; **2:** 319–35.
11 MacCarty CS, Brown DN. Orbital tumours in children. *Clin Neurosurg* 1964; **11:** 76–93.
12 Templeton AC. Orbital tumours in African children. *Br J Ophthalmol* 1971; **55:** 254–61.
13 Henderson JW. *Orbital tumours.* 2nd ed. Stuttgart: Dekker, 1980; 377–86.
14 Crawford JS. Disease of the orbit. In: Crawford JS, Morin JD, eds. *The eye in childhood.* New York: Grune and Stratton, 1983: 331–64.
15 Mortada A. Non-lipoid and lipoid reticulo-endotheliosis of orbital bones. *Am J Ophthalmol* 1966; **61:** 558-60.
16 Pearlstone AD, Flom L. Letterer-Siwe's disease. *J Pediatr Ophthalmol* 1970; **7:** 103-5.
17 Beller AJ, Kornbleuth W. Eosinophilic granuloma of the orbit. *Br J Ophthalmol* 1951; **35:** 220-5.
18 Truhlsen SM. Eosinophilic granuloma involving the orbit. Report of a case. *Am J Ophthalmol* 1954; **37:** 571-5.
19 Chawla HB, Cullen JF. Eosinophilic granuloma of the orbit. *J Pediatr Ophthalmol* 1968; **5:** 93-5.
20 Straatsma BR. Eosinophilic granuloma of bone. *Trans Am Acad Ophthalmol Otolaryngol* 1958; **62:** 771-6.
21 Baghdassarian SA, Shammas HF. Eosinophilic granuloma of orbit. *Ann Ophthalmol* 1977; **9:** 1247-51.
22 Nirankari MS, Singh M, Manchanda SS, Chitkara NL, Maudgal MC. Eosinophilic granuloma of the orbit. *Arch Ophthalmol* 1957; **58:** 857-61.
23 Wheeler M. Exophthalmos caused by eosinophilic granuloma of bone. *Am J Ophthalmol* 1946; **29:** 980-4.
24 Heuer HE. Eosinophilic granuloma of the orbit. *Acta Ophthalmol (Kbh)* 1972; **50:** 160-5.
25 Bray PT. Histiocytosis X: In Deeley TJ, ed. *Modern radiotherapy and oncology. Malignant disease in childhood.* London: Butterworth, 1974: 372-94.

26 Sims DG. Histiocytosis X. Follow-up of 43 cases. *Arch Dis Child* 1977; **52:** 433-40.
27 Mozziconacci P, Offret G, Forest A, *et al.* Histiocytose X avec lésions oculaires. Étude anatomique. *Ann Pediat (Paris).* 1966; **13:** 348-55.
28 Epstein DL, Grant WM. Secondary open angle glaucoma in histiocytosis X. *Am J Ophthalmol* 1977; **84:** 332-6.
29 Mittleman D, Apple DJ, Goldberg MF. Ocular involvement in Letterer-Siwe disease. *Am J Ophthalmol* 1973; **75:** 261-5.
30 Rupp RH, Holloman KR. Histiocytosis X affecting the uveal tract. *Arch Ophthalmol* 1970; **84:** 468-70.
31 Zimmerman LE. Ocular lesions of juvenile xanthogranuloma: nevoxanthoendothelioma, *Trans Am Acad Ophthalmol Otolaryngol* 1965; **69:** 412-42.
32 Heath P. The ocular features of a case of acute reticuloendotheliosis (Letterer-Siwe type). *Trans Am Ophthalmol Soc* 1959; **57:** 290-302.
33 Anderson B, Margolis G, Lynn WS. Ocular lesions related to disturbance in fat metabolism. *Am J Ophthalmol* 1958; **45** (suppl): 23-41.
34 Lahav M, Albert DM. Unusual ocular involvement in acute disseminated histiocytosis X. *Arch Ophthalmol* 1974; **91:** 455-8.
35 Kepes JJ, Kepes M. Predominantly cerebral forms of histiocytosis X. *Acta Neuropathol (Berl)* 1969; **14:** 77-98.
36 Feinberg SB, Langer LO. Roentgen findings of increased intracranial pressure and communicating hydrocephalus as insidious manifestations of chronic histiocytosis X. *AJR* 1965; **95:** 41-7.
37 Takahashi M, Martel W, Oberman HA. The variable roentgenographic appearance of idiopathic histiocytosis. *Clin Radiol* 1966; **17:** 48-53.
38 Foucar E, Rosai J, Dorfmann RF. The ophthalmologic manifestations of sinus histiocytosis with massive lymphadenopathy. *Am J Ophthalmol* 1979; **87:** 354-67.
39 Friendly DS, Font RL, Rao NA. Orbital involvement in sinus histiocytosis. *Arch Ophthalmol* 1977; **95:** 2006-11.
40 Sanders TE, Miller JE. Infantile xanthogranuloma of the orbit. *Trans Am Acad Ophthalmol Otolaryngol* 1965; **69:** 458-64.
41 Gaynes PM, Cohen GS. Juvenile xanthogranuloma of the orbit. *Am J Ophthalmol* 1967; **63:** 755-7.
42 Smith DG, Nesbit ME, D'Angio GJ, Levitt SH. Histiocytosis X: role of radiation therapy in management with special reference to dosage levels employed. *Radiology* 1973; **106:** 419-22.
43 Cohen M, Zornoza J, Cangir A, Murray JA, Wallace S. Direct injection of methyl prednisolone sodium succinate in the treatment of solitary eosinophilic granuloma of bone. A report of nine cases. *Radiology* 1980; **136:** 289-93.
44 Broadbent V, Davies EG, Heaf D, *et al.* Spontaneous remission of multisystem histiocytosis X. *Lancet* 1984; **i:** 253-4.
45 Osband ME, Lipton JM, Lavin P, *et al.* Histiocytosis X: demonstration of abnormal immunity, T-cell histamine H2-receptor deficiency and successful treatment with thymic extract. *N Engl J Med* 1981; **304:** 146-53.
46 Davies EG, Levinsky RJ, Butler M, Broadbent V, Pritchard J, Chessells JM. Thymic hormone therapy for histiocytosis X. *N Engl J Med* 1983; **309:** 493-4.
47 Thomas JA, Janossy G, Chilosi M, Pritchard J, Pincott JR. Combined immunological and histochemical analysis of skin and lymph node lesions in histiocytosis X. *J Clin Pathol* 1982; **35:** 327-37.
48 Lahey ME. Histiocytosis X: An analysis of prognostic factors. *J Pediatr* 1975; **87:** 184-9.

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Polyunsaturated fatty acids and diabetic retinopathy

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SUMMARY One hundred and forty nine diabetic patients were ophthalmologically assessed seven years after randomisation to a low carbohydrate or modified fat diet (rich in linoleic acid). Glycaemic control, regardless of the type of diet, was a major determinant of the development of retinopathy. Poorly controlled patients (haemoglobin A1c >8%) with low levels of linoleic acid in cholesterol ester had a significantly greater frequency of retinopathy than well controlled patients or patients with similarly unsatisfactory control but higher levels of linoleic acid. The findings support an earlier suggestion that linoleic acid might protect against diabetic retinopathy.

Most diabetic patients in western countries have until recently been advised to follow a low carbohydrate diet. Such diets are invariably relatively high in fat, but little attention has been paid to the type of fat eaten.[1] Evidence of the beneficial effect of dietary fibre on glycaemic control has led to a change in diabetic dietary policy in several countries. Diabetics are now advised that at least half their daily energy intake should come from fibre rich complex carbohydrates.[2] There is still no firm recommendation concerning the optimal sources of fat, and most diabetics derive the bulk of their fat calories from saturated animal fat.

There are several reasons why diabetics might benefit if an appreciable proportion of dietary fat is polyunsaturated. Polyunsaturated fatty acids (PUFA) have a cholesterol lowering effect which might reduce the risk of cardiovascular disease, which is particularly high among diabetics.[3] In addition PUFA apparently have some antithrombotic effect (and in particular an action reducing platelet aggregation) at least partly because they are precursors of certain prostaglandins.[4,5] Finally, Houtsmuller *et al.*[6] have suggested that in non-insulin dependent diabetics a diet rich in PUFA taken for three to six years might delay the development and progression of retinopathy during that time. A study in which maturity onset diabetics were randomised between two types of dietary advice varying in PUFA intake provides a test for the hypothesis of Houtsmuller *et al.*

Material and methods

Patients. In 1973 a prospective study of newly diagnosed maturity onset diabetics referred to the Radcliffe Infirmary Diabetic Clinic was started.[7] Between 1973 and 1976 250 patients were recruited and then randomised to advice on either a standard low carbohydrate diet (LC) or a diet with a modified fat intake (MF), the details of which are given below. To be considered for entry patients had to be less than 66 years old and untreated except, in some cases, for some general dietary advice from their general practitioners. Excluded were patients on any treatment that would grossly disturb carbohydrate metabolism, who had an imminently life threatening condition, or who were reckoned clinically to require insulin treatment immediately. The presence (or past history) of any other endocrine disease, angina pectoris, or neurological deficit following a cerebrovascular accident precluded admission, as did the presence, but not a past history, of liver disease.

All the patients in the original study were invited to the Oxford Eye Hospital for a review of ophthalmological findings in 1982. One hundred and fifty of the original cohort of 250 attended. Of the remaining 100, 22 had died, 20 had moved or emigrated, and 58 declined the invitation to attend for ophthalmological review. One attender had cataracts preventing funduscopy and photography and was therefore excluded from all analyses. The ophthalmological features of the 100 non-attenders differed at entry to the trial from the patients who agreed to be re-examined. In addition those examined were older,

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Table 1 *Comparison of features before treatment and known liability to retinopathy of those attending and not attending ophthalmological review in 1982*

	Reviewed (n=149)	*Not reviewed (n=100)*	*p*
Age (years)	57·8±0·8	48·7±1·2	0·001
Sex, % male	55	41	NS
Body mass index (BMI)	27·7±0·5	29·8±0·5	0·02
History of symptoms before entry (months)	4·3±1·2	8·6±1·6	0·05
Fasting glucose (mmol/l)	11·8±0·33	11·4±0·4	NS
Number with retinopathy at diagnosis	3	14	
Number without retinopathy at diagnosis	136	46	
Number without full ocular examination at diagnosis	10	40	

NS=not significant at 5% level.

less obese, and had a shorter history of symptoms at diagnosis than those not examined seven years later (Table 1). However, the two groups did not then differ significantly as to sex or in fasting blood glucose. Of the 149 patients 78 (52%) were initially assigned to LC and 71 (48%) to MF. The diet groups were well matched for age, sex, and body mass index.

Dietary advice. At diagnosis the patients were advised to follow either a classical low carbohydrate diabetic diet or a relatively high carbohydrate, modified fat diet.[7] The advised energy intake was determined according to percentage above ideal body weight. In LC the advice was to restrict carbohydrate to a maximum of 40% of total energy. Protein provided up to 20% and fat about 40% total energy with a ratio of PUFA to saturated fatty acids (P:S) about 0·3. MF was originally designed to be a lipid lowering diet. It was therefore advised that fats should provide no more than 30% total energy (with a P:S ratio of 0·9 or above). Protein once again provided about 20% and carbohydrate in this diet about 50% of total energy. Cholesterol was restricted to a maximum of 2·1 g weekly.

On review in 1982 each patient was interviewed by a dietitian who took a full dietary history with particular reference to the amount and type of fat and carbohydrate. On the basis of the dietary interview and their known randomisation, but without knowledge of any clinical data, she divided the patients according to whether she believed them to be complying faithfully with the principles of the dietary advice (compliers) or not (non-compliers). Thirty nine of the 79 (49%) allocated to LC and 19 out of the 70 (27%) allocated to MF were considered to be compliers. At this assessment initial dietary advice was reinforced, as it had been intermittently at outpatient visits since diagnosis.

Ophthalmological assessment. At the time of diagnosis all patients were assessed by a consultant ophthalmologist (P.A.). The ophthalmological assessment included visual acuity and ophthalmoscopic examination of the fundus. In patients with retinopathy each feature of the retinopathy (that is, exudate, microaneurysm, haemorrhage, and new vessels) was compared with the Hammersmith series of colour photographs grade B and noted to be either absent or less than, the same as, or more than standard photo B. At the 1982 assessment the patient's fundi were also photographed with a Zeiss fundus camera and Ektachrome 64 film. Eight 30° views were taken to include disc, macula, nasal to disc, and temporal to macula, and four diagonal views about the disc. In patients with background retinopathy this was quantified in detail by creating a montage of the fundus with a back projection system, in which each microaneurysm, new vessel, cotton wool spot, exudate, and haemorrhage was colour coded and drawn on an acetate sheet. The numbers of microaneurysms, cotton wool spots, and new vessels were counted and the areas of exudate and haemorrhage measured by computer planimetry. A retinopathy index[8] was devised by adding the scores for each feature and then calculating a weighted index. Even one microaneurysm on the fundus photograph resulted in a positive classification for retinopathy.

Metabolic assessment. A detailed metabolic assessment was made initially and at one, three, and five years after diagnosis. The data presented here relate to selected measurements at these times as well as to the time of the 1982 ophthalmological assessment when, in addition, a random blood sample was taken for measurement of blood glucose, haemoglobin A1c, total cholesterol, and cholesterol in the various lipoprotein fractions, and fatty acid composition of the cholesterol esters.[9 10] Cholesterol ester rather than triglyceride fatty acids were studied, since (unlike the triglycerides) this fraction is uninfluenced by the fact that fasting samples were not available. Haemoglobin A1c, total and subfraction cholesterols are similarly little influenced by diurnal variation. Triglycerides were not measured because of the marked difference when studied in the non-fasting state.

Results

No MF complier had retinopathy at diagnosis. Thirty eight of the 39 compliant patients on LC had been recorded free of retinopathy at diagnosis, but no fundal assessment was recorded then for the other one. In the 1982 review this patient had only one microaneurysm. At the seven-year ophthalmological

Table 2 *Frequency of retinopathy among compliers and non-compliers according to dietary advice*

	Low carbohydrate			*Modified fat*		
	No retinopathy	*Retinopathy*	*Total*	*No retinopathy*	*Retinopathy*	*Total*
Compliers	23 (59%)	16 (41%)	39	15 (79%)	4 (21%)	19
Non-compliers	28 (70%)	12 (30%)	40	28 (55%)	23 (45%)	51
Total	51 (65%)	28 (35%)	79	43 (61%)	27 (39%)	70

Table 3 *Fatty acid composition of the cholesterol esters in patients on LC and MF (mean % of total ± SD)*

	All patients			*Compliers*		
	LC	*MF*	*p*	*LC*	*MF*	*p*
C16:0	9±2·8	8±2·1	NS	9±3·3	7±1·6	0·051
C16:1	6±3·2	5±2·3	0·045	5±2·4	4±1·7	0·037
C18:0	1±2·5	1±2·7	NS	1±2·7	1±2·2	NS
C18:1	16±4·0	13±3·7	0·002	15±3·3	11±2·5	0·001
C18:2	40±8·6	46±8·4	0·001	39±9·3	45±10·2	0·043
C18:3	0·5±2·6	0·5±2·7	NS	0·5±2·6	0·5±2·2	NS
C20:4	6±3·7	6±2·8	NS	6±3·7	6±2·0	NS

assessment those patients complying with MF tended to have retinopathy less often than LC compliers (21% versus 41%) or the non-compliers, but this difference was not statistically significant ($\chi^2=2{\cdot}25$, Table 2).

Diabetic control. No significant difference between LC and MF was found in glycaemic control as measured either by the mean fasting glucose one, three, and five years after diagnosis, or HbA1c, or random glucose at ophthalmological review. Dividing the patients into compliers and non-compliers still did not identify any difference between the diet groups in these factors. More notably, when all 149 patients were considered together, the presence of retinopathy correlated with the fasting glucose level at diagnosis, the mean of values of fasting glucose at one, three, and five years, and also with random glucose and haemoglobin A1c levels measured at the 1982 review. (These results are presented in detail elsewhere.[11])

Treatment. Patients entered into the study did not require insulin initially, but subsequently 22 (15%) have been started on insulin and 73 (49%) patients on oral hypoglycaemic agents, so 55 (37%) have continued on diet alone. The frequency of retinopathy was higher in the insulin and tablet treated patients (45% and 46% respectively) than in those continuing on diet alone (22%). This difference could be related to higher blood glucose levels in the insulin and tablet treated groups.

Table 4 *% of linoleic acid in cholesterol esters in various groups of patients*

	Retinopathy	*No retinopathy*
Modified fat diet (all patients)	45±7 (24)	46±9 (37)
Modified fat diet (compliers)	42±8 (5)	46±11 (13)
Low carbohydrate diet (all patients)	39±9 (22)	40±9 (49)
Low carbohydrate diet (compliers)	38±9 (15)	39±10 (19)

Lipid results. Patients advised to follow MF had significantly lower levels of total cholesterol over the five years of follow-up than LC (cholesterol mean± SD at years 1 3, and 5: 187±35 mg/dl on MF and 211±37 mg/dl on LC, p<0·001) (SI: 4·8±0·91 mmol/l on MF and 5·5±0·96 mmol/l on LC). At the time of diagnosis cholesterol levels in the two groups were identical. The fatty acid composition of the plasma cholesterol esters measured at the ophthalmological review also differed appreciably on the two diets (Table 3). Levels of linoleic acid were higher on MF than LC, but levels of myristic and oleic acid were higher on LC. Patients with retinopathy tended to have a lower percentage of linoleic acid in cholesterol esters than those without retinopathy, but there were no significant differences in fatty acid composition of cholesterol ester between these two groups of patients (Table 4).

Houtsmuller *et al.*[6] found virtually no retinopathy among their diabetics whose percentage of linoleic acid in cholesterol esters exceeded 50%. Their patients were all described as 'poorly controlled.' In our patients glycaemic control is a major determinant of retinopathy. We therefore divided patients according to both glycosylated haemoglobin and percentage of cholesterol esters as linoleate (Table 5). Poorly controlled patients (HbA1c >8%, our upper limit of normal) with cholesterol ester linoleate

Table 5 *Frequency of retinopathy according to haemoglobin A1c and % of linoleic acid in cholesterol ester*

	Haemoglobin A1c >8%		*Haemoglobin A1c >8%*	
	Retinopathy	*No retinopathy*	*Retinopathy*	*No retinopathy*
Cholesterol ester C18:2 >50%	6 (37%)	10 (63%)	3 (20%)	12 (80%)
Cholesterol ester C18:2 <50%	24 (53%)	21 (47%)	10 (21%)	37 (79%)
Total	30 (49%)	31 (51%)	13 (21%)	49 (79%)

<50% had a significantly greater frequency of retinopathy than the remaining patients ($\chi^2=10\cdot5$, $p<0\cdot005$). In patients with relatively good glycaemic control (HbA1c <8%) levels of linoleic acid appear not to influence the frequency of retinopathy. A similar trend is seen if, rather than haemoglobin A1c, fasting blood glucose at one, three, and five years is used to distinguish well controlled from poorly controlled patients.

Discussion

In 1979 Houtsmuller and colleagues described a dramatic reduction in the development of retinopathy among diabetic patients with poor glycaemic control who ate diets high in polyunsaturated fatty acids. Over a six-year period they found that 92% of patients on a diet low in linoleic acid showed the development or progression of retinopathy. Among those on a diet rich in PUFA minimal progression of retinopathy was reported.[6]

Despite the fact that a proportion of the original cohort could not be followed up, our data provide some confirmation that linoleic acid protects against the development of retinopathy, but the results are not as striking as the earlier report, possibly for two reasons. First, our patients did not show as high a level of linoleic acid in the cholesterol esters, probably because they ingested less linoleate than the Dutch. It may be that a higher proportion of linoleate is necessary for demonstrable benefit. Second, blood glucose control is a major determinant of retinopathy,[11] and the effect of linoleic acid may be less marked with tighter rather than with looser glycaemic control. The precise relationship between the effects of glycaemia and linoleic acid on retinopathy is likely to be complex and may require a study of larger numbers of patients to disentangle separate effects.

At the time of ophthalmological reassessment all our patients were given dietary reinforcement. We hope thus to increase linoleic acid levels in patients recommended MF and so test more adequately whether linoleic acid indeed protects against retinopathy during the next two years of follow-up.

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References

1 Mann JI. Diet and diabetes. *Diabetologia* 1980; **18:** 89–95.
2 Nutrition Subcommittee of the British Diabetic Association's Medical Advisory Committee. Dietary recommendations for the 1980s—a policy statement by the British Diabetic Association. *Human Nutrition: Applied Nutrition* 1982; **36A:** 378–86.
3 Jarrett RJ. Diabetes and the heart: coronary heart disease. *J Endocrinol (Oxf)* 1977; **6:** 389–402.
4 Renaud S, Morazain R, Godsey F. Platelet functions in relation to diet and serum lipids in British farmers. *Br Heart J* 1981; **46:** 562–70.
5 Gerrard JM, White JG. Labile aggregation stimulating substance, free fatty acids and platelet aggregation. *J Lab Clin Med* 1976; **87:** 73–82.
6 Houtsmuller AJ, Zahn KJ, Henkes HE. Unsaturated fats and progression of diabetic retinopathy. *Doc Ophthalmol* 1979; **48:** 363–71.
7 Hockaday TDR, Hockaday JM, Mann JI, Turner RC. A prospective comparison of modified fat-high carbohydrate with standard low-carbohydrate dietary advice in the treatment of diabetes: a one year follow-up study. *Br J Nutr* 1978; **39:** 357–62.
8 Holman RR, Dornan TL, Mayon-White R. Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. *Lancet* 1983; **i:** 204–8.
9 Jones DB, Carter RD, Haitas B, Mann JI. Low phospholipid arachidonic acid levels in diabetic platelets. *Br Med J* 1983; **286:** 173–5.
10 Moore RA, Oppert S, Eaton P, Mann JI. Triglyceride fatty acids confirm a change in dietary fat. *Clin Endocrinol (Oxf)* 1977; **7:** 143–9.
11 Howard-Williams J, Hillson RM, Bron A, Awdry P, Mann JI, Hockaday TDR. Retinopathy is associated with higher glycaemia in maturity-type onset diabetes. *Diabetologia* 1984; **27:** 198–202.

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Autoimmunity in hereditary retinal degeneration. I. Basic studies

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SUMMARY One hundred and sixteen patients with retinitis pigmentosa (RP), 64 patients with other eye diseases, and 36 control subjects with no known eye disease were examined for antiretinal autoimmune activity. Sera were screened by indirect immunofluorescence on normal donor human eye sections to detect antibodies to human retinal antigens. Forty three of 116 RP patients (37%), 21 out of 64 non-RP patients with other eye diseases (33%), and 1 out of 42 controls (2%) had antibodies reacting with donor eye retinal antigens. Lymphocytes were tested by an in vitro transformation assay to detect cell mediated immunity to retinal antigens. Sixteen RP patients (19%), 11 non-RP patients (18%), and four controls (10%) showed lymphocyte sensitisation. Autoimmune responses were detected in many degenerative ocular disorders, but it is not known if they play a contributory pathogenic role.

Over the past 10 years various studies have examined the role of the immune system in retinitis pigmentosa (RP), a group of hereditary retinal degenerative disorders characterised by pigmentary retinopathy, progressive visual field loss, and nyctalopia. In 1973 Rahi reported that these patients had raised levels of serum IgM, though no specificity was assigned to the antibody.[1] Spiro *et al.* failed to confirm Rahi's findings but suggested that the discrepancy may have been from variations in methods, antisera, environmental influences, and composition of the RP groups used in the two studies.[2] Spalton *et al.* using immunofluorescence techniques showed the binding of sera from RP patients to rat photoreceptor cells.[3] Keltner *et al.* recently reported one case of photoreceptor degeneration in a cancer patient who had serum antibodies reactive with normal retinal tissue on the immunofluorescent complement fixation test.[4]

A number of studies have been made to look at cell mediated immunity in retinal degenerations. Lymphocytes from 17 out of 23 patients with retinal degenerative disease were cytotoxic to retinoblastoma cells in tissue culture, which indicates immune reactivity against retinal antigens by these patients.[5] Retinoblastoma cells have previously been shown to contain some antigens present on normal photoreceptor cells.[6] Rocha and Antunes showed cell mediated immunity in 34 out of 50 RP patients with the use of the migration inhibition factor test.[7] Brinkman *et al.* using transformation and migration inhibition assays showed sensitisation to retinal antigens of lymphocytes from RP patients.[8] A study by Heredia *et al.* showed sensitisation to retinal antigens in 26 out of 45 RP patients and presented evidence that lymphocytes from these patients also had a reduced response to phytohaemagglutinin in vitro and had diminished suppressor cell activity.[9]

While autoimmune activity has been well recorded in RP patients, it is not known whether it is specific to certain types of RP or how commonly it occurs in other types of retinal degeneration and ocular disease. To determine the extent and specificity of immune mechanisms active in a number of retinal degenerative disorders two tests of immune function were evaluated in blood samples from patients with RP, patients with non-RP ocular disease, and normal control subjects. The RP type was diagnosed as specifically as possible for each patient.

Materials and methods

Patients with progressive panretinal degenerations were evaluated with a comprehensive medical, ocular, and family history (pedigree analysis); ophthalmological examination; and tests consisting of Goldmann visual fields, electroretinogram, dark

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adaptation final rod threshold, fundus photography, and fluorescein angiography.

The patients with hereditary retinal degenerations were classified as precisely as possible by the above tests and examination results by means of previously published methods and rationale[10-14] and placed in RP subgroups of: rod-cone and cone-rod degeneration by inheritance, choroideremia, preserved para-arteriole retinal pigment epithelium RP, pigmented paravenous retinochoroidal atrophy, and Usher syndrome.

Other retinal degenerations tested included congenital stationary nightblindness, Stickler's syndrome, luetic chorioretinitis, choroiditis, and sympathetic ophthalmia. These diseases were tested as an aid to understanding the specificity of the immunological responses. The control group consisted of volunteers with no known eye problems.

10 ml of peripheral venous blood was drawn into plain tubes for serum samples and 30 ml into heparinised tubes for isolation of lymphocytes. Blood was drawn from 116 RP patients, 64 non-RP patients with other eye disorders, and 42 normal volunteers without eye disorders who had given informed consent.

Isolation of serum and lymphocytes. Blood drawn for serum samples was allowed to clot and was centrifuged at 2000 rpm for 10 min. Then the serum was removed and stored at −20°C until testing.

To isolate lymphocytes blood was centrifuged at 2000 rpm for 10 min. The buffy coat was removed, diluted with an equal volume of RPMI 1640 (Flow Laboratories, Inglewood, California), and layered on to 5 ml cushions of Ficoll-paque (Pharmacia Fine Chemicals, Piscataway, New Jersey). After centrifugation at 2000 rpm for 20 min the layer of cells at the interface was recovered, washed three times in RPMI 1640, and stored in freezing medium (RPMI 1640, 10% DMSO, 10% glycerol, 10% sterile, heat inactivated human AB serum) at −70°C until testing.

Immunofluorescence. Serum samples were tested by the method of Sainte-Marie[15] to detect circulating antibodies to retinal antigens. A positive control consisted of human retinal sections incubated with rabbit antibody to human retina. A negative control consisted of human retinal sections incubated with saline in place of serum in the first step. Direct staining of sections with fluorescein conjugated goat antihuman IgG and IgM (Meloy, Springfield, Virginia 22151) was carried out to determine that there were no immunoglobulins bound to the retina prior to incubation with sera. Sera from patients and controls were examined for the presence of antibodies by means of fluorescein conjugated goat antihuman IgG and IgM.

In vitro transformation assays. Lymphocytes were tested by in vitro transformation assays with the use as antigens of crude human retinal extract (250, 100, and 50 μg/ml; 20 μl/well), and a bovine rod outer segment preparation (250, 100, and 50 μg/ml; 20 μl/well).[16] Mitogens used to test functional viability of lymphocytes were concanavalin A (Miles-Yeda Ltd, Rehovot, Israel), 100 μg/ml; 20 μl/well, and phytohaemagglutinin (Difco Laboratories, Detroit, Michigan), 100 μg/ml; 20 μl/well. (μg/ml = mg/l.) The lymphocytes were incubated with the mitogens for three days or with antigens for six days at 37°C in a 5% CO_2 atmosphere. Tritiated thymidine (specific activity 25 mCi/mmol) 10 μCi/well (Amersham, Arlington Heights, Illinois) was added four hours prior to harvesting. Results are expressed as a stimulation index (SI) calculated as:

$$\mathrm{SI} = \frac{\text{counts per minute in presence of antigen}}{\text{counts per minute in absence of antigen}}.$$

This ratio allows for comparison of results from one assay to another. A stimulated index $>2{\cdot}0$ was considered an indication of cell mediated activity against retinal antigens.[8]

The results of the immunofluorescence and sensitisation tests were analysed statistically for the three groups (RP patients, patients with non-RP eye problems, controls with no known eye problems) with the use of the χ^2 test and analysis of variance. Statistical review was done by Coralee Yale of the UCLA Department of Biostatistics.

Results

Table 1 summarises the results of indirect immunofluorescence testing of sera from patients and controls. Forty three of 116 RP patients (37%) showed antibodies to retinal antigens. The antibodies were not restricted to one particular type of retinitis pigmentosa but rather were seen in all types examined so far. Twenty one of 64 patients with non-RP eye disorders (33%) also developed antibodies to retinal antigens in their serum. One of the 42 normal controls (2%) had circulating antiretinal antibodies. The intensity of staining varied from weak to strong, but even weakly stained sections could be distinguished readily from those in which staining was absent (Figs. 1–3). Staining was seen most frequently in the rod outer segments, though sera from several patients also reacted with cell membranes either in the outer nuclear layer or, more often, throughout the entire retina.

Transformation assays. Results of in vitro transformation assays (Table 1) indicated sensitisation to retinal antigens in 16 out of 86 RP patients (19%), 11 out of 64 patients with other eye diseases (17%), and 4 out of 42 controls (10%). There was no difference in mitogen response between patients and controls.

Nine of the RP patients showing sensitisation in the transformation assays also developed circulating antiretinal autoantibodies. Five of the non-RP

Table 1 *Patients with autoantibodies to retinal antigens and/or sensitisation to retinal antigens*

Patient	*Diagnosis*	*Immuno-fluorescence staining*		*Stimu-lation index*
		IgG	*IgM*	
*Retinitis pigmentosa (RP) type**				
1	Preserved para-arteriolar retinal pigment epithelium (PPRPE)	+	–	1·6
2	PPRPE	–	+	1·4
3	PPRPE	+	+	NT
4	PPRPE	–	+	1·4
5	Simplex rod-cone	+	+	2·7
6	Simplex rod-cone	–	–	2·2
7	Simplex rod-cone	+	+	2·5
8	Simplex rod-cone	–	–	2·3
9	Simplex rod-cone	+	–	2·7
10	Simplex rod-cone	+	–	1·4
11	Simplex rod-cone	–	+	1·7
12	Simplex rod-cone	+	+	NT
13	Simplex rod-cone	+	+	1·1
14	Simplex rod-cone	+	+	NT
15	Simplex rod-cone	+	–	2·1
16	Simplex rod-cone	–	–	2·1
17	Simplex rod-cone	+	+	0·3
18	Multiplex rod-cone	–	+	1·6
19	Simplex cone-rod	–	+	2·5
20	Simplex cone-rod	+	+	2·0
21	Simplex cone-rod	–	–	2·8
22	Simplex cone-rod	–	+	2·8
23	Autosomal recessive rod-cone	+	+	1·1
24	Autosomal recessive rod-cone	–	+	1·6
25	Autosomal recessive rod-cone	+	+	1·6
26	Autosomal recessive rod-cone	–	+	1·4
27	Autosomal recessive rod-cone	–	–	3·4
28	Autosomal recessive cone-rod	–	+	2·1
29	Autosomal dominant rod-cone	+	+	1·7
30	Autosomal dominant rod-cone	–	+	1·5
31	Autosomal dominant rod-cone	+	+	1·7
32	Autosomal dominant cone-rod	–	+	NT
33	X-linked recessive rod-cone	–	+	1·5
34	X-linked recessive rod-cone	+	+	1·1
35	X-linked recessive rod-cone	–	–	2·3
36	X-linked recessive rod-cone	–	+	1·5
37	X-linked recessive rod-cone	–	+	1·5
38	X-linked recessive cone-rod	+	–	1·1
39	Choroideremia	+	–	1·1
40	Choroideremia	+	–	2·4
41	Choroideremia	+	–	NT
42	Choroideremia	–	+	1·5
43	Choroideremia	+	–	2·4
44	Usher syndrome	+	–	1·1
45	Usher syndrome	–	+	1·6
46	Usher syndrome	–	–	3·8
47	Usher syndrome	–	+	1·6
48	Usher syndrome	–	+	1·5
49	Simplex cone-rod	–	+	1·5
50	Simplex cone-rod	–	+	1·2
51	Leber's amaurosis	–	+	1·4
52	Congenital RP with macular colobomata	+	+	NT

Table 1 *Patients with autoantibodies to retinal antigens and/or sensitisation to retinal antigens*—continued

Patient	*Diagnosis*	*Immuno-fluorescence staining*		*Stimu-lation index*
		IgG	*IgM*	
Patients with non-RP ocular disease†				
1	Choroiditis	+	+	1·4
2	Stickler syndrome	+	+	2·3
3	Measles retinopathy	+	–	1·0
4	Sympathetic ophthalmia	+	–	1·0
5	Regional RPE/choroidal atrophy	+	–	3·4
6	Luetic chorioretinitis	+	+	1·1
7	Luetic chorioretinitis	–	+	1·4
8	Congenital stationary night blindness	+	–	2·3
9	Macular oedema	+	–	0·4
10	Cystoid macular oedema	–	–	3·0
11	Macular hole	+	–	0·1
12	Macular degeneration	–	–	2·2
13	Macular degeneration	–	+	2·0
14	Cataract	+	+	1·5
15	Cataract	+	+	2·3
16	Cataract/retinal detachment	–	+	1·2
17	Glaucoma/macular degeneration	–	–	2·0
18	High myopia	–	+	1·1
19	High myopia	–	–	3·8
20	Detached retina	–	+	1·6
21	Retinal break	–	–	2·8
22	Toxoplasmosis	+	+	1·5
23	Toxoplasmosis	+	+	1·3
24	Fundus flavimaculatis	–	–	2·5
25	Diabetic retinopathy	+	–	1·3
26	Chorioretinitis	+	–	0·7
27	Uveitis	+	+	1·1
Normal‡				
1		–	+	2·1
2		–	–	3·0
3		–	–	3·3
4		–	–	2·2

NT = No cells available for testing.

*There were 64 patients with negative indirect immunofluorescence and stimulation index <2·0 with the following diagnoses: PPRPE (1), pigmented paravenous retinochoroidal atrophy (5), simplex rod-cone (15), multiplex rod-cone (1), simplex cone-rod (7), recessive rod-cone (9), dominant rod-cone (2), dominant cone-rod (1), X-linked rod-cone (7), choroideremia (4), Usher syndrome (8), congenital RP with macular colobomata (2), sector RP (1), Albers-Schonberg (1), RP/diabetes/renal failure (1).

†There were 37 patients with negative indirect immunofluorescence and stimulation index <2·0 with the following diagnoses: Congenital stationary night blindness (1), macular oedema (1), macular/retinal degeneration (9), cataract (2), retinal tear (1), fundus flavimaculatus (1), diabetic retinopathy (3), birdshot chorioretinitis (2), surface wrinkling retinopathy (1), dominant optic atrophy (1), vitreous degeneration (1), hydroxychloroquine toxicity (1), retinal vasculitis (4), carrier X-linked (1), chorioretinitis (3), panretinal degeneration (1), RPE degeneration (1), high myopia (1).

‡There were 38 normal volunteers with no indirect immunofluoresence or stimulation index >2·0.

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patients and one control also showed both sensitisation and positive immunofluorescence. Results of both tests are summarised in Table 2.

Antibodies reactive with retinal antigens were present in significantly more RP and non-RP patients (p = 0·001) when each group was compared with the

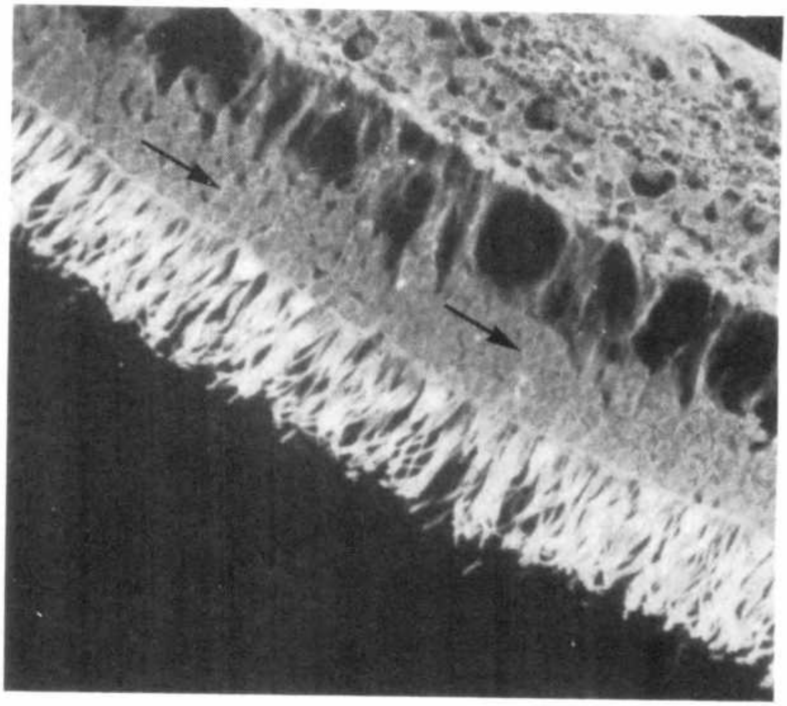

Fig. 1 *Indirect immunofluorescence on normal human retina showing IgM autoantibodies in serum from patient with PPRPE. Heavy staining of rod outer segments and a generalised lighter staining of outer nuclear cell membranes* (arrows) *can be seen* (× 235).

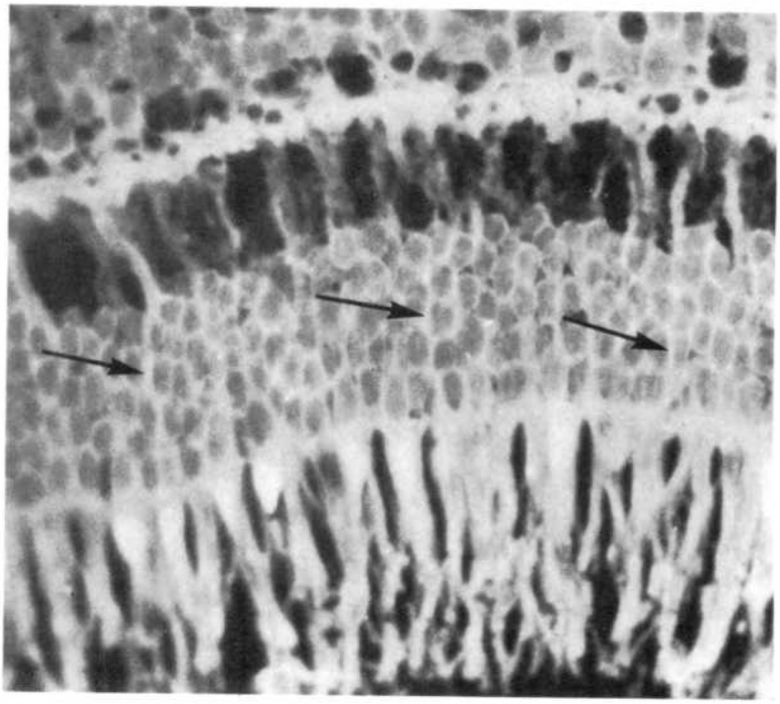

Fig. 2 *Indirect immunofluorescence on normal human retina showing IgG autoantibodies in serum from patient with X-linked recessive cone-rod degeneration. Note strong staining* (arrows) *of cell membranes in outer nuclear layer* (× 235).

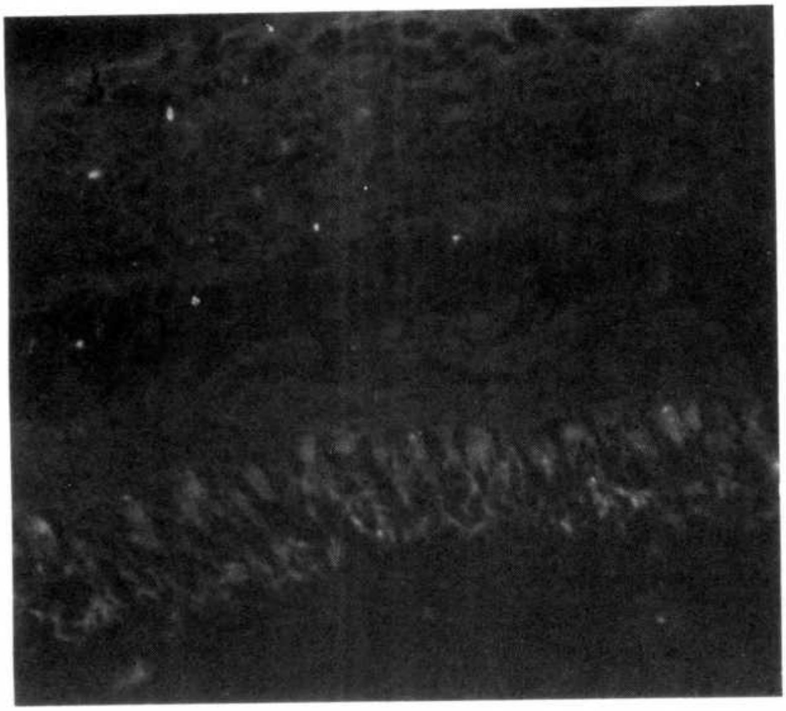

Fig. 3 *Indirect immunofluorescence on normal human retina showing lack of staining with serum taken from normal control. Autofluorescence of the cones is evident in this section (× 235).*

Table 2 *Summary of immune responses to retinal antigens*

	*RP patients**	*Non-RP patients†*	*Normal controls*
Autoantibodies	43/116 (37%)	21/64 (33%)	1/42 (2%)
Sensitisation	16/85 (19%)	11/64 (18%)	4/42 (10%)
Autoantibodies and sensitisation	9/86 (10%)	5/64 (8%)	1/42 (2%)

*RP = Retinitis pigmentosa.
†Non-RP = Eye disease other than retinitis pigmentosa.

control group, but the incidence of antibodies to retinal antigens in the two patient groups did not differ significantly ($p = 0\cdot7622$). The transformation assay, which indicates sensitisation of the cell mediated arm of the immune response, was not significantly different in any of the three groups: RP versus non-RP $p = 0\cdot8668$, RP versus normal $p = 0\cdot3963$, non-RP versus normal $p = 0\cdot4312$. Because of the small number of patients in each diagnostic category so far it was not possible to show significant differences between responses of patients with specific disease types with the use of either test of immunological function.

Discussion

Autoimmune mechanisms have been found to be associated with many diseases involving degenerative processes (for example, inflammatory bowel disease, multiple sclerosis, thyroiditis, rheumatoid arthritis, autoimmune haemolytic anaemia). Even though they may not be the primary cause of a disease, they can aggravate a degenerative process by immunopathological mechanisms thereby causing the normally protective role of the immune system to turn into a destructive one.

Recent studies in RP evaluating immune responses to retinal antigens suggest the possibility that the immune system may contribute to the retinal degenerative process.[1–3, 5–9] Our results from the screening of sera to detect antibodies to retinal antigens indicate that autoimmune mechanisms are active in many patients with ocular degenerative disorders. A statistically significant ($p<0\cdot001$) number of patients with both RP and non-RP eye disorders have circulating antibodies with activity directed towards retinal antigens as compared with normal controls. The transformation assays, which detect sensitised lymphocytes and indicate cellular rather than humoural mechanisms, showed no differences between patients and controls. If immune mechanisms do contribute to retinal ocular degeneration, it is more likely that they do so by the production of cytotoxic antibodies than by cell mediated mechanisms.

Though an analysis of variance was done to evaluate the various ocular degenerative disorders, no pattern has emerged as yet with respect to differences in immune reactivity in the various types of degeneration. The autoimmune response appears to be an associated response with all types of ocular degeneration. We did note, however, several staining patterns on indirect immunofluorescence, in which specific parts of the retina are selectively involved (rod outer segments only, membranes only, or both membranes and rod outer segments). Further studies looking at differential staining patterns may eventually correlate with some disease types.

Patients with pigmented paravenous retinochoroidal atrophy (PPRCA) were grouped arbitrarily with the RP subgroups, since all these patients had a pigmentary retinopathy, and some of them showed a progressive retinal degeneration. However, it should be noted that many PPRCA patients have stationery disease, and the PPRCA is a degenerative pattern in which the common finding in all cases is retinal paravenous degenerative disease.[17] Evaluation of the immune status of the PPRCA group was believed to be particularly pertinent, since the pathogenic mechanism for the paravenous degeneration is not understood.

Evidence of autoimmune reactivity in response to retinal antigens was found in 21 out of 64 non-RP patients and four control subjects in our studies. It is not surprising that such reactions are taking place in eye disorders other than RP, since immune reactions are seen frequently in eye disorders (for example, uveitis, sympathetic ophthalmia). The statistically significant difference between patients and controls showing antiretinal activity suggests that the immune reaction in these patients may be related to their retinal degeneration. The immune reactivity in normal controls and patients with non-retinal ocular problems could reflect a cross reactivity between antigens in the retina and other tissues.

Our preliminary studies thus provide evidence of autoimmune activity in RP of all types as well as other ocular degenerative disorders. Whether these mechanisms play a pathological role clinically has not yet been shown. If autoimmune mechanisms are shown to play a pathogenic role in the degenerative process, and if criteria can be established for therapeutic immunosuppression without endangering the health of the patient, it may be possible to slow the degenerative process in selected patients who show strong autoimmune reactivity against retinal components.

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References

1 Rahi AHS. Autoimmunity and the retina. II. Raised serum IgM levels in retinitis pigmentosa. *Br J Ophthalmol* 1973; **57:** 904–9.

2 Spiro R, Weleber R, Kimberling W. Serum IgM in retinitis pigmentosa—a genetic study. *Clin Genet* 1978; **13:** 295-304.

3 Spalton DJ, Rahi AHS, Bird AC. Immunologic studies in retinitis pigmentosa associated with retinal vascular leakage. *Br J Ophthalmol* 1978; **62:** 183-7.

4 Keltner JL, Roth AM, Chang RS. Photoreceptor degeneration: Possible autoimmune disorder. *Arch Ophthalmol* 1983; **101:** 564–9.

5 Char DH, Bergsma DR, Rabson AS, Albert DM, Herberman RB. Cell mediated immunity to retinal antigens in patients with pigmentary retinal degenerations. *Invest Ophthalmol Visual Sci* 1974; **13:** 198–203.

6 Feldberg NT, Donoso LA. Surface and cytoplasmic antigens in retinoblastoma. *Invest Ophthalmol Visual Sci* 1980; **19:** 1242–5

7 Rocha H, Antunes L. Primary retinitis pigmentosa—autoimmunity? *Metabolic Ophthalmol* 1977; **1:** 153–6.

8 Brinkman CJJ, Pinckers AJLG, Broekhuyse RM. Immune reactivity to different retinal antigens in patients suffering from retinitis pigmentosa. *Invest ophthalmol Visual Sci* 1980; **19:** 743–50.

9 Heredia CD, Vich JM, Huguet J, Garcia-Calderon JV, Garcia-Calderon PA. Altered cellular immunity and suppressor cell activity in patients with primary retinitis pigmentosa. *Br J Ophthalmol* 1981; **65:** 850-4.

10 Heckenlively JR. The classification of retinitis pigmentosa. *Acta XXIV Congress of ophthalmology.* Philadelphia: Lippincott, 1983; **1:** 34–7.

11 Heckenlively JR. The hereditary retinal degenerations. In: Emory A, Rimoin D, eds. *Principles and practice of medical genetics.* Edinburgh: Churchill, 1983: 522–38.

12 Heckenlively JR, Martin DA, Rosales TO. Telangiectasia and optic atrophy on cone-rod degenerations. *Arch Ophthalmol* 1981; **99:** 1983–91.

12 Heckenlively JR. Preserved periarteriole retinal pigment epithelium (PPRPE) in retinitis pigmentosa. *Br J Ophthalmol* 1982; **66:** 26–30.

14 Pearlman JT, Kamin DF, Kopelow SM, Saxton J. Pigmented paravenous retinochoroidal atrophy. *Am J Ophthalmol* 1975; **80:** 630–5.

15 Sainte-Marie G. A paraffin embedding technique for studies employing immunofluorescence. *J Histochem Cytochem* 1962; **10:** 250–6.

16 Chant SM, Meyers-Elliott RH. Autoimmunity: A possible factor in the development of retinal degeneration in the RCS rat. *Clin Imunol Immunopathol* 1982; **22:** 419–27.

17 Heckenlively JR, Kokame G. Pigmented paravenous retinochoroidal degeneration: Electrophysiological findings. *Doc Ophthalmol Proc Ser* in press.

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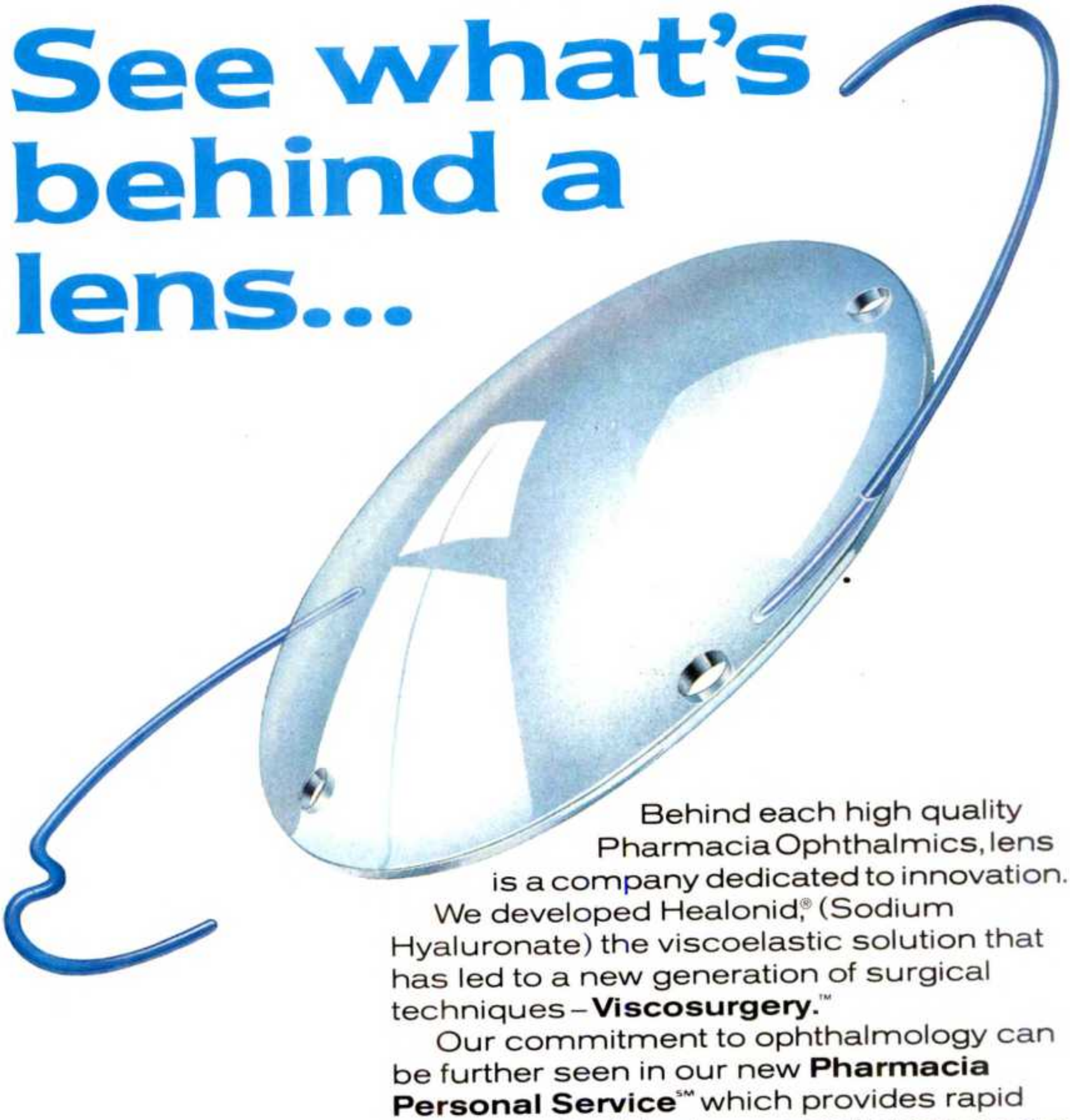

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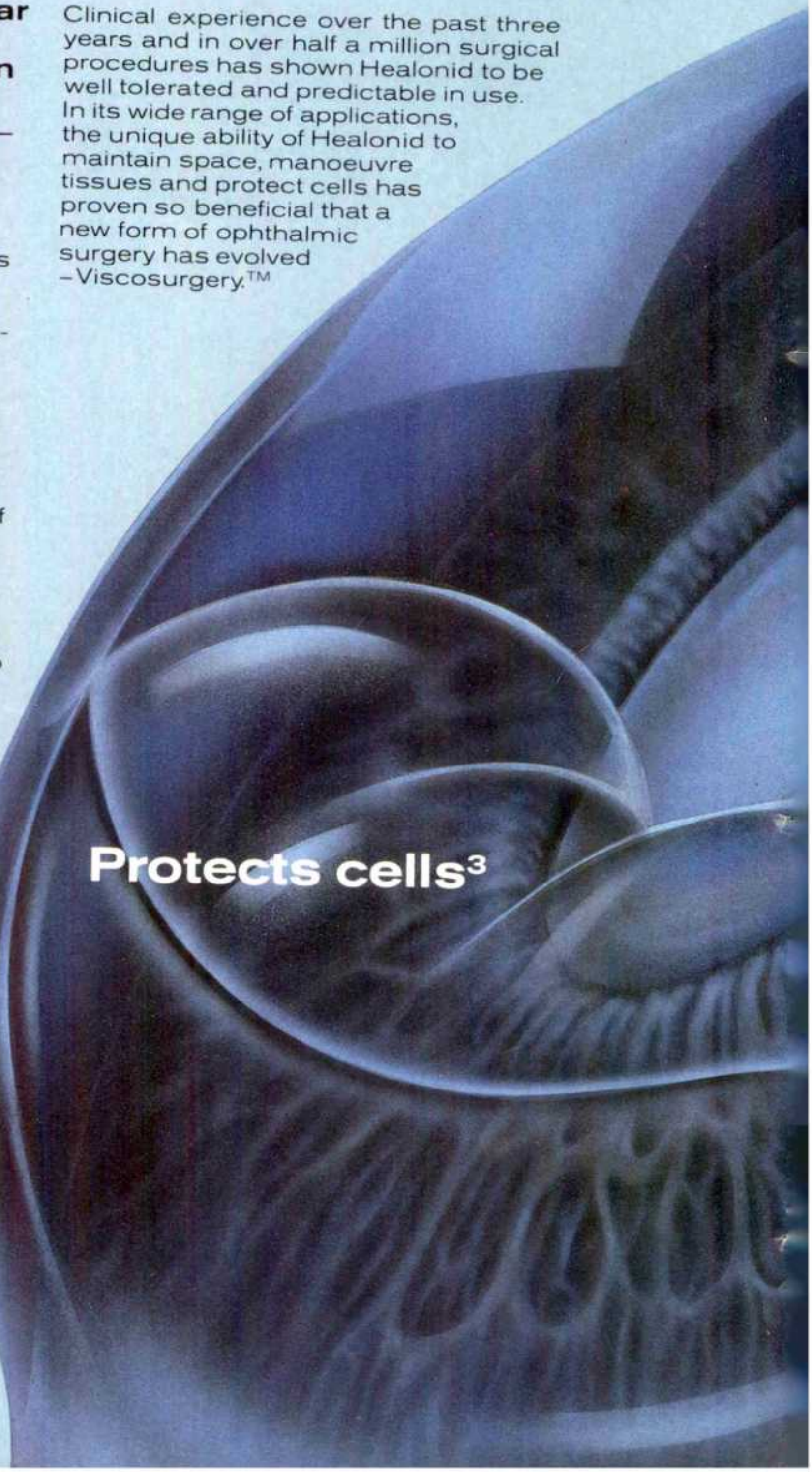

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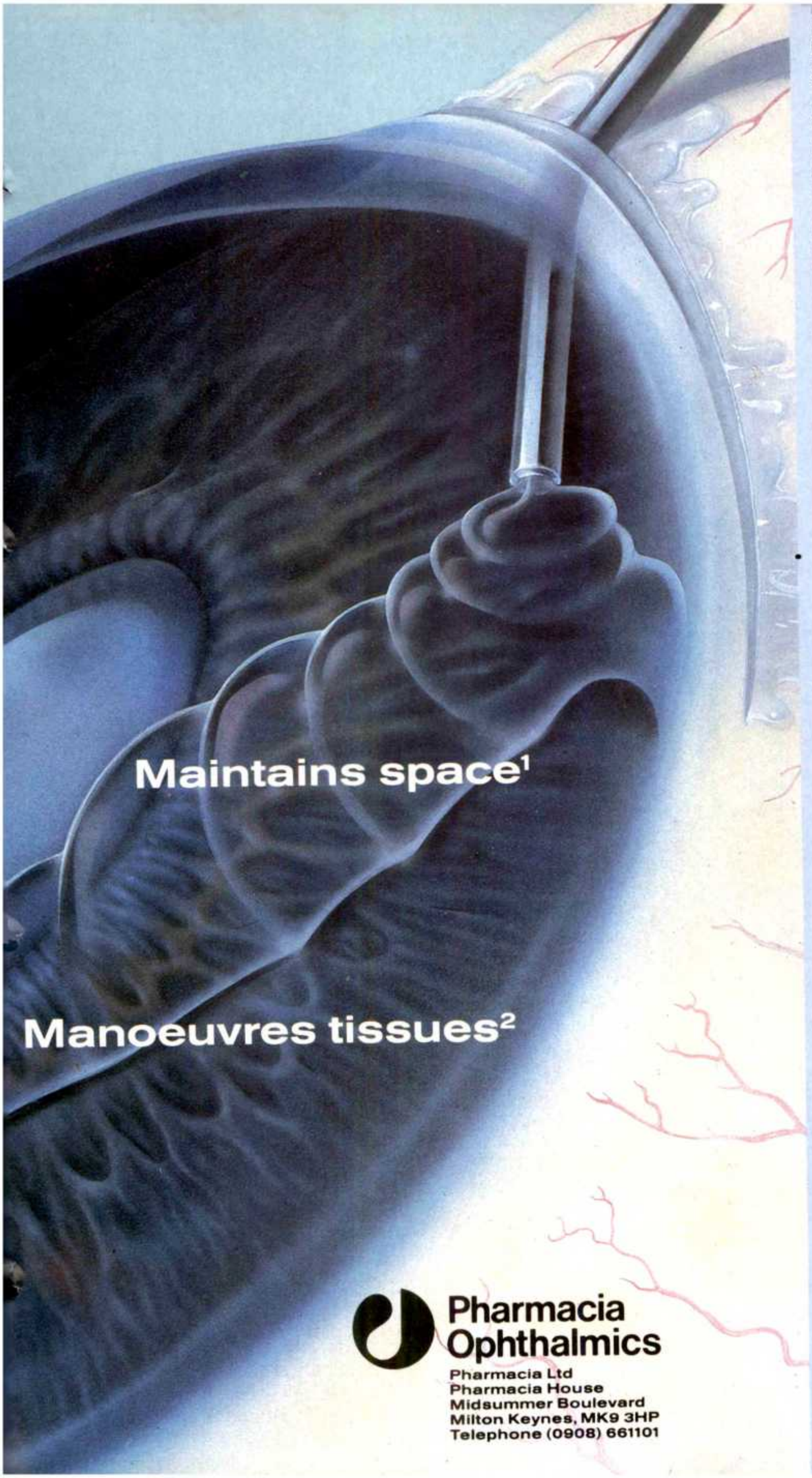

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PRESCRIBING TABLE

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Introduction of HEALONID into the anterior or posterior chamber keeps tissues separated during the operative procedure and protects them from trauma from other tissues or instruments. The anterior chamber depth is maintaned, vitreous bulge can be reduced, and the loss of irreplaceable endothelial cells which inevitably accompanies surgery can be greatly reduced.

INDICATIONS
Surgical procedures on the eye, including intraocular lens insertion, intra and extra capsular lens extraction, glaucoma surgery, corneal graft, surgery for accidental trauma, retinal detachment and vitreal replacement procedures.

DOSAGE AND ADMINISTRATION
The syringe is assembled and made ready for use according to the instruction sheet with each syringe. The indication for use will govern the timing and quantity of HEALONI used. See data sheet for Healonid Monograph.

PRECAUTIONS
The anterior chamber should not be overfilled with HEALONID, except in glaucoma surgery. At close of surgery some of the HEALONID should be removed by irrigation or aspiration. Intraocular pressure should be monitored during the post operative period and any excessive rises treated with appropriate therapy.

CONTRA-INDICATIONS, WARNINGS
There are no known contra-indications to HEALONID. Because the drug is extracted from avian tissues, despite rigorous purification procedures minute amounts of protein are present, and thus the remote possibility of idiosyncratic reactions remains.

ADVERSE REACTIONS
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PHARMACEUTICAL PRECAUTIONS
Store at 2-8°C protected from light and freezing. Shelf life 3 years.

LEGAL CATEGORY POM.

PACKAGING QUANTITIES AND BASIC N.H.S. PRICE (6th April 1984) Disposable syringes containing 0.4ml £29.44 each.

FURTHER INFORMATION
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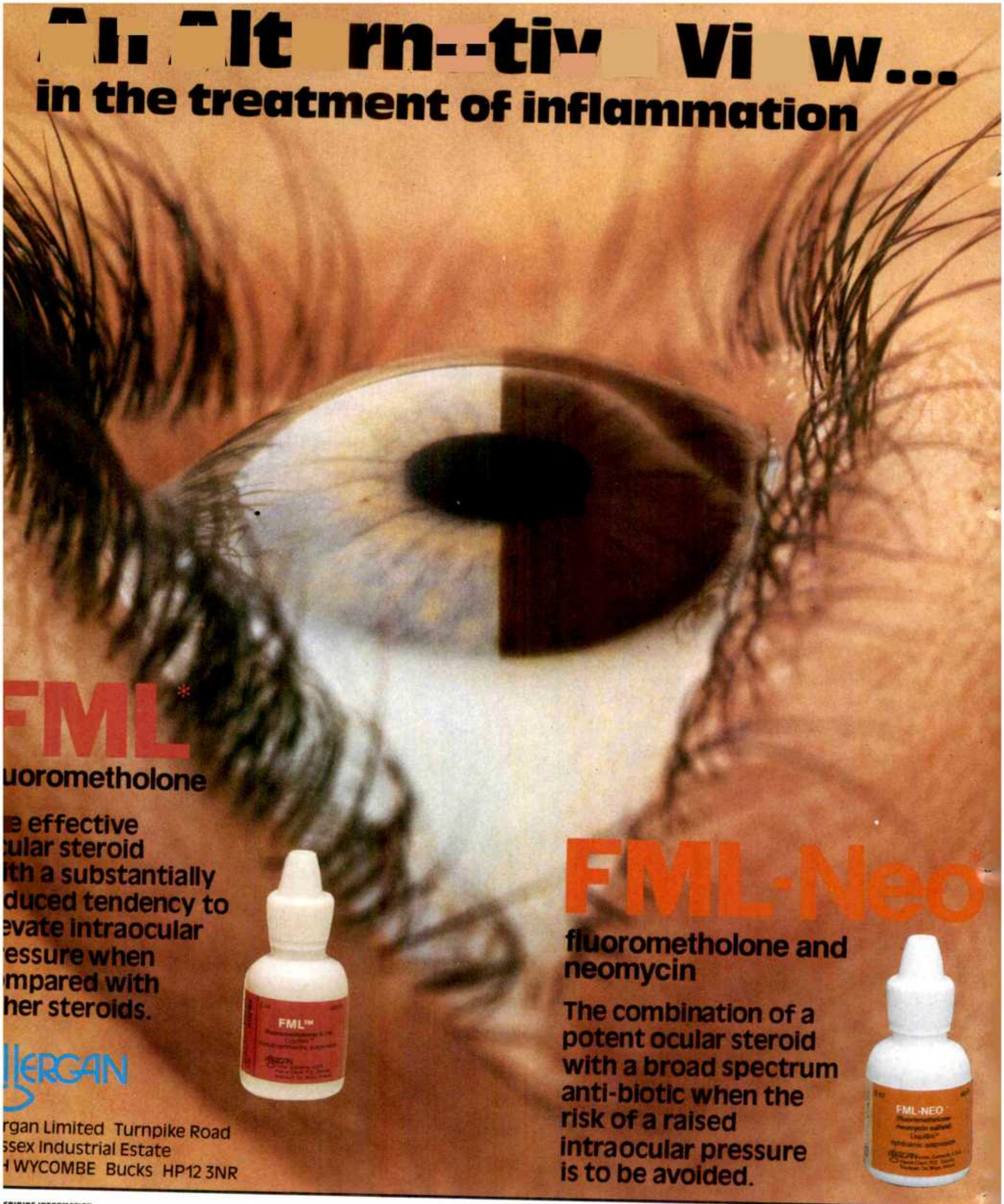

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fluorometholone and neomycin

The combination of a potent ocular steroid with a broad spectrum anti-biotic when the risk of a raised intraocular pressure is to be avoided.

CRIBING INFORMATION
ion White, microfine, sterile ophthalmic suspension containing fluorometholone (0.1%). **Uses** Topical ophthalmic
for steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the
age and Administration 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to
e dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely.
ications, Warnings, etc. CONTRA-INDICATIONS. Acute superficial herpes simplex keratitis. Fungal diseases of ocular
Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity
tituents of this medication. **Warnings** Steroid medication in the treatment of herpes simplex keratitis (involving the
uires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the
defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of
ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or
oration has been known to occur with use of topical steroids. Safety and effectiveness have not been demonstrated in
the age group two years or below. This preparation contains benzalkonium chloride and should be used with caution in
with hydrophilic contact lenses. **Use in Pregnancy** Safety of the use of topical steroids during pregnancy has not been
Precautions As fungal infections of the cornea are particularly prone to develop coincidentally with long-term steroid
s, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intra
sure should be checked frequently. **Adverse Reactions** Glaucoma with optic nerve damage, visual acuity or field defects,
ubcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of
ocal side-effects of steroid therapy ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin.
utical Precautions Protect from freezing. **Legal Category** POM. **Package Quantities** Supplied in plastic dropper
ml and 10ml. Basic NHS cost (as at July 1984) 5ml £1.78, 10ml £2.83. PL 0426/0028. Full prescribing information is available

FML-NEO* PRESCRIBING INFORMATION
Presentation Sterile, white, microfine ophthalmic suspension containing fluorometholone, NF0.1% and neomycin sulphate, BP0.5% (equivalent to 0.35% neomycin base). **Uses** FML-NEO* is indicated for the management of steroid responsive inflammation of the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe, when threatened or complicated by infection with neomycin-sensitive organisms. **Dosage and Administration** One or two drops in the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to discontinue treatment prematurely. Shake well before using. **Contra-indications, Warnings etc.** Acute untreated purulent ocular infections. Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the conjunctiva and cornea. Ocular tuberculosis, fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As for FML* above and, in addition in diseases due to micro-organisms resistant to neomycin, infection may be masked enhanced or activated by the steroid. Prolonged use may result in overgrowth of nonsusceptible organisms. Articles in current medical literature indicate an increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If sensitivity or other untoward reactions occur, discontinue the medication. **Precautions** Patients with histories of herpes simplex keratitis should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated. Local side effects of steroid therapy ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not freeze. **Legal Category** POM. **Package Quantities** Available in 5ml plastic dropper bottles. Basic NHS cost (as at July 1984) £1.90. PL 0426/0045. Full Prescribing information is available on request.

*Trade Mark

FMNE 3

British Journal of Ophthalmology, 1985, **69**, 25–28

Distribution of tetracycline in the conjunctiva of patients on long term systemic doses

P N DILLY[1] AND I A MACKIE[2]

From the [1]Department of Anatomy, St George's Hospital Medical School, London; and the [2]Department of Ophthalmology, St George's Hospital, London

SUMMARY After oral administration of tetracycline fluorescence has been detected in biopsy specimens taken from human and animal conjunctiva. The fluorescence is not uniform but appears to be concentrated in the goblet cells, around the blood vessels, and in a thin film on the external surface of the epithelium. Immersion studies suggest there is a selective binding to the surface of the conjunctiva.

The last decade has seen the increasing use of systemic tetracycline in ophthalmology. It is used in a maintenance dose of 500 mg or 250 mg a day and often without current topical ocular medication. Therapy is often continued over many months and may be maintained for an indefinite period in sight threatening conditions. It usually takes a number of weeks for the effects of treatment to be seen.

'Oral tetracycline is the cornerstone of therapy in acne rosacea' states Wearing.[1] Its use in ocular rosacea was reported by Marmion as early as 1969,[2] but further reports on its use in this condition did not appear until 1978.[3] Its other obvious use is in chronic staphylococcal blepharoconjunctivitis,[4] but it is increasingly being used in allergic and other non-infective diseases of the conjunctiva of a grossly inflammatory nature.

It is interesting that Sneddon[5] writing on a clinical trial of tetracycline in (skin) rosacea in 1966 remarked that 'unheralded by any fanfares, tetracycline as a method of treatment has come into current use in the last few years', although there was 'in fact virtually no published work on the subject.' The same could be said now of its use in ophthalmology.

It probably works either because of its antibacterial properties, or because it has an anti-inflammatory action independent of the well known antimicrobial effects, or both. Several reports have shown tetracycline to be effective in skin diseases in which micro-organisms play no part in the pathogenesis.[6–9] The localisation of systemic tetracycline in the conjunctiva is not known. As a preliminary study to the investigation of the means by which tetracycline might affect the biodynamics of the conjunctiva we have investigated the distribution of tetracycline in the conjunctiva in patients on long term tetracycline for eye disease.

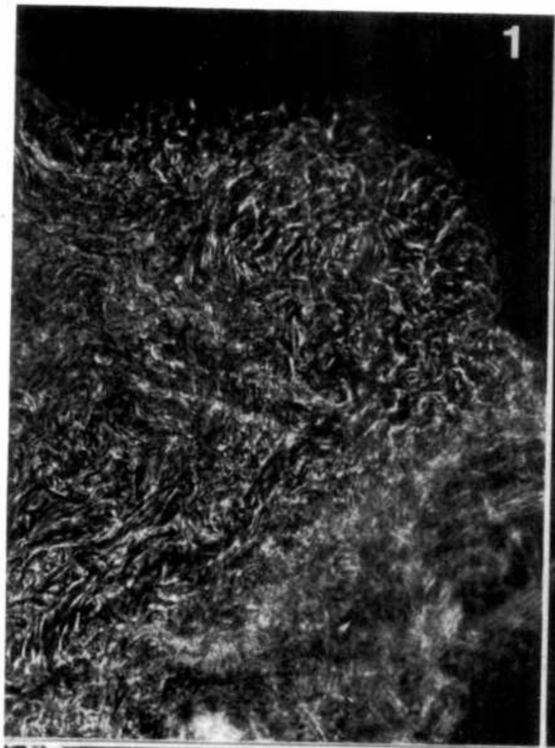
Materials and methods

After informed consent biopsy specimens were obtained from the lower eyelid conjunctiva of five patients who had received at least 250 mg of oral tetracycline daily for at least one year and from two patients who had never had tetracycline.

The biopsies were obtained by anaesthetising the lower lid with an injection of 2% lignocaine without adrenaline. A 2 mm Elliot trephine was used, and the biopsies were taken from the middle of the palpebral conjunctiva of the lower lid. A portion of the tarsal plate was included to give stability to the tissue. Great care is needed to avoid handling the conjunctival surface of the specimen. The specimens were immersed in normal saline and immediately transported to the laboratory and frozen by putting the specimens in a pot of pentane that was floating in a Dewar flask of liquid nitrogen.

Sections were cut at 10 µm on a Bright cryostat and mounted on glass slides. The sections were examined with a Zeiss fluorescence microscope with filters of the blue excitation range 450–490 nm. The controls were similarly treated. The photographs were taken with an exposure time of 30 s with a Kodak Tri-X film which was developed in Kodak HC110 developer.

Correspondence to Mr Ian A Mackie, FRCS, 99 Harley Street, London W1N 1DF.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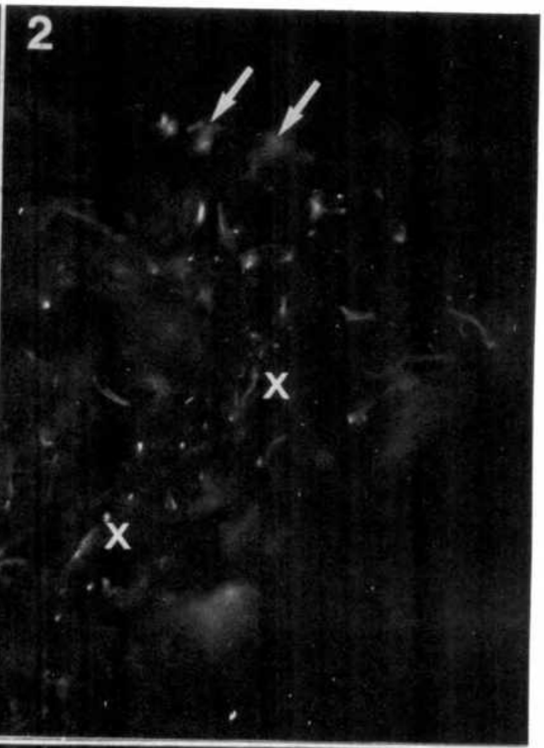
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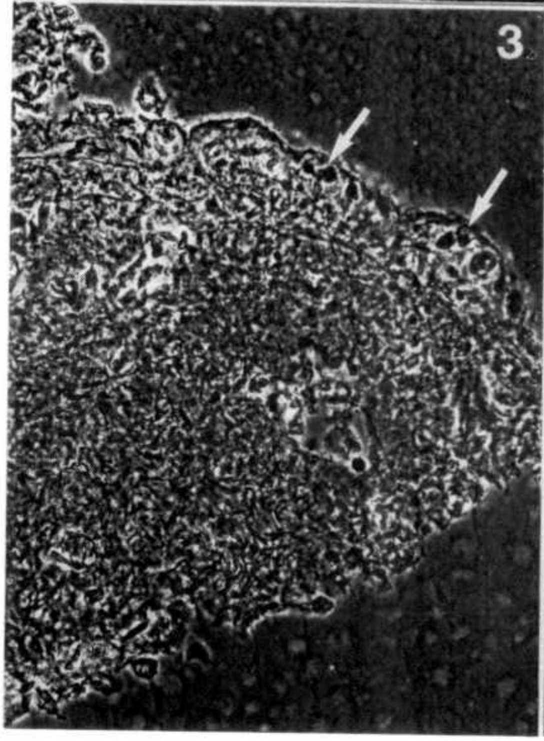
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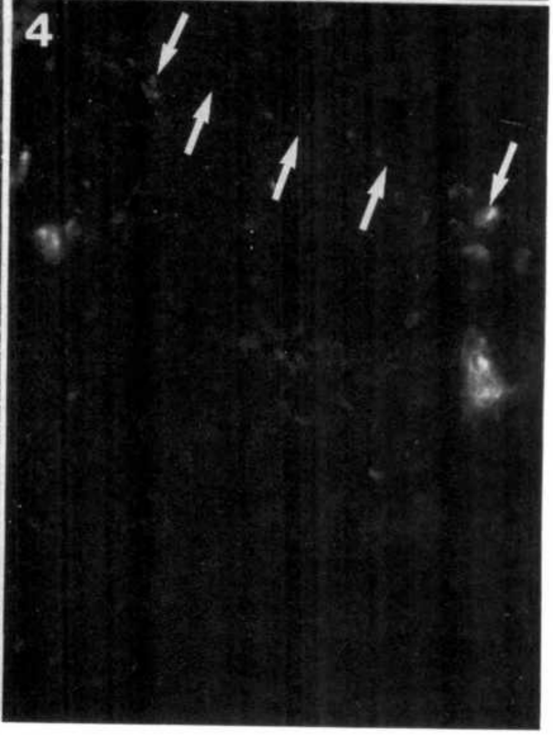
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Combined phase contrast microscopy made the handling, orientation, and identification of the sections and recognition of the regions of fluorescence simpler.

Fresh sections of conjunctiva that had not previously been exposed to tetracycline either systemically or locally were immersed in tetracycline eye drops for five hours. The control sections were immersed in saline. They were then washed by gently changing the immersion solution to normal saline. The normal saline was allowed to stand for five minutes before it was replaced. The saline was changed five times before the specimens were examined. Some specimens were left overnight in a large volume of saline that was gently agitated. Fresh post-mortem conjunctivae were also obtained and similarly treated. We could detect no significant difference between the responses of material from the two sources.

The animal material came from guinea-pigs and rats. The tetracycline (2 mg/kg) was administered daily for periods of up to 100 days.

Results

Tetracycline fluorescence was detected in the conjunctiva of all the patients who had taken tetracycline orally. There was no fluorescence in the control group.

The fluorescence was not generalised but was restricted to a thin film-like layer on the surface and to small areas in the surface layer of cells. In the deeper layers of the conjunctiva there were also regions showing strong fluorescence (Figs. 1–4).

The surface fluorescence was globular and that of the deeper structures much more linear in overall shape (Figs. 2, 4).

SURFACE FLUORESCENCE

Control sections of conjunctiva did not autofluoresce. In sections of specimens taken from patients who had taken systemic tetracycline fluorescence occurred all along the surface layers of the conjunctiva, but it was most concentrated in the goblet cells. The goblet cell fluorescence penetrated the whole extent of the cell and both the nucleus and the cytoplasm appeared to fluoresce equally. The general surface fluorescence, however, was only a simple narrow line rather like a membrane some 0·5 μm thick.

In the deeper layers of the stroma the fluorescence was patchy and usually linear in outline. The fluorescence was of a similar intensity to that found in the surface region. Sometimes the fluorescence was in the form of a circular profile. Phase contrast microscopy revealed that these regions contained blood vessels, and that the fluorescence occurred in the areas surrounding blood vessels. This fluorescence around blood vessels resembled that reported from the skin of rats on high doses of systemic tetracycline.[10]

The more linear regions of fluorescence in these deeper layers are associated either with blood vessels that have been sectioned longitudinally or with the inner region of the epithelial cell layers. Sometimes, however, it is not possible to see with the phase contrast microscope any significant morphological difference between those cells that show fluorescence and the surrounding cells (Figs. 1, 2).

We can say little about the rate of accumulation of tetracycline in the conjunctiva of man. But in our experiments with guinea-pigs and rats it is much slower than in the skin. In a preliminary experiment with guinea-pigs we have found tetracycline given by intraperitoneal injection at 2 mg/kg body weight to appear in the skin after six days but still be undetectable in the conjunctiva after 26 days. The time scale in rats for tetracycline to appear in the conjunctiva is somewhat shorter, but it can still be detected in the skin before it can be found in the eye.

Sections of human conjunctiva that were immersed in tetracycline eye drops and washed showed fluorescence in the goblet cells and a thin layer along the surface, indicating that the tetracycline was localised in the goblet cells and surface layer (Fig. 4). This fluorescence was not removed by repeated gentle washing, and probably represents a binding of the tetracycline to some component of the mucus

Fig. 1 *Phase contrast micrograph of the same section as Fig. 2 for orientation. (×300).*

Fig. 2 *Fluorescence micrograph of the same section as Fig. 1. Some of the goblet cells are indicated* (arrows). *The linear and punctate deeper fluorescence is indicated by* X. *The fluorescence is produced by tetracycline in the tissue. The section was taken from a biopsy from a patient who had been taking 250 mg tetracycline orally for over 18 months. (×300).*

Fig. 3 *Phase contrast micrograph of the same section as Fig. 4. Some of the goblet cells in the surface layer are indicated by arrows. (×300).*

Fig. 4 *Fluorescence micrograph of the same section as Fig. 3. The surface layer of fluorescence is well seen as is the binding within goblet cells* (arrows). *Some deeper structures have also absorbed tetracycline and are fluorescing. Fifty-two-hour immersion in tetracycline eye drops in physiological, isotonic, and isosmotic saline. (×300).*

secreted by the goblet cells. Whether or not this role is played by the goblet cells in vivo is not known.

We did not detect any significant fluorescence in the basal layer of the epithelium.

Discussion

The conjunctiva is an epidermal derivative, and these results demonstrate that it has several similar properties to other epidermal structures in its response to tetracycline. Marks and Davies[10] demonstrated that the fluorescence produced by tetracycline in skin was best seen in the basal layer of the epidermis, the sebaceous glands, and the hair follicles and was preferentially concentrated in parakeratotic areas. They showed also that it remained detectable in the skin after stopping administration and suggested that there was a preferential uptake in cells with a high rate of replication. They observed that the tetracycline did not just diffuse through the dermis and epidermis but was in some way bound to some cellular structures. They suggested that this binding might play a significant part in its therapeutic role.

We have demonstrated a similar binding in the conjunctiva, and it is probable that similar pharmacological effects occur as those in the skin.

The mode of action is unknown, but it is probably not exclusively antimicrobial, because several of the diseases improved by tetracycline therapy are not caused by bacteria. It has recently been demonstrated that tetracycline may have anti-inflammatory properties[11] quite apart from its antibacterial action.

The thin layer of fluorescence at the surface of the conjunctiva may represent a surface film of tetracycline secreted by the goblet cells. It is known that tetracycline appears in the skin surface film after oral administration of the drug.[12] It could, of course, be that this thin layer is the remnant of the tear film all of which contains tetracycline, and that this thin layer has survived processing.

The patchy distribution of tetracycline in the conjunctiva suggests that as in the skin the passage of the drug through the conjunctiva is not just simply by diffusion. The association with blood vessels may be nothing more than a reflection of the fact that the tetracycline is blood borne from the gut. This may be the region at which tetracycline is presented in its highest concentrations to the conjunctiva, and the drug diffuses out from here. The tetracycline can get to the goblet cells in the surface layer of the conjunctiva, either by being secreted on to the surface of the eye by the lacrimal or meibomian glands or, by diffusing through the conjunctival epithelium. When it reaches the goblet cells it must in some way be absorbed and concentrated. The surface film too may arrive either by secretion from associated glands, the direct diffusion on to the surface through the conjunctival epithelium, or, as seems more likely to us, by being secreted by the goblet cells along with their mucus on to the surface.

If the immersion experiment results do indicate binding of tetracycline to the mucus layer in contact with the surface of the eye, then this may be a mechanism whereby the tetracycline is prevented from being washed from the surface of the eye by the flow of tears. The preliminary animal experiment results suggest that tetracycline accumulates more slowly in the conjunctiva than in the skin.

We acknowledge the technical expertise of Miss Celia Cope. Our thanks are owed to Mrs G. Coulton who typed the manuscript.

References

1 Wearing GO. Acne rosacea. In Fraunfelder FT, Roy FH, eds. *Current ocular therapy*. Philadelphia: Saunders, 1980: 147–8.
2 Marmion UJ. Tetracycline in the treatment of ocular rosacea. *Proc R Soc Med* 1969; **62:** 11–2.
3 Brown SI, Shahinian L Jr. Diagnosis and treatment of ocular rosacea. *Ophthalmology* 1978; **85:** 779–86.
4 Smolin G. Staphylococcal blepharitis. In Frauenfelder FT, Roy FH, eds. *Current ocular therapy*. Philadelphia: Saunders, 1980: 434–5.
5 Sneddon IB. A clinical trial of tetracycline in rosacea. *Br J Dermatol* 1966; **78:** 649–53.
6 Piamphongsant T. Tetracycline for the treatment of pityriasis lichenoides. *Br J Dermatol* 1974; **91:** 319–22.
7 Chan HL. Panniculitis (Rothmann-Makia) with good response to tetracycline. *Br J Dermatol* 1975; **92:** 351–4.
8 Sneddon IB. The treatment of steroid induced rosacea and perioral dermatitis. *Dermatologica* 1976; **152:** (suppl 1) 231–7.
9 Thomsen K, Osterbye P. Pustulosis palmaris et plantaris. *Br J Dermatol* 1978; **89:** 273–96.
10 Marks R, Davies MJ. The distribution in the skin of systemically administered tetracycline. *Br J Dermatol* 1969; **81:** 448–51.
11 Elewski BE, Lamb BAJ, Sams WM, Gammon WR. In vivo suppression of neutrophil chemotaxis by systemically and topically administered tetracycline. *J Am Acad Dermatol* 1983; **8:** 807–812.
12 Rashleigh PL, Rife E, Goltz RW. Tetracycline levels in skin surface film after oral administration of tetracycline to normal adults and to patients with acne vulgaris. *J Invest Dermatol* 1967; **49:** 611–5.

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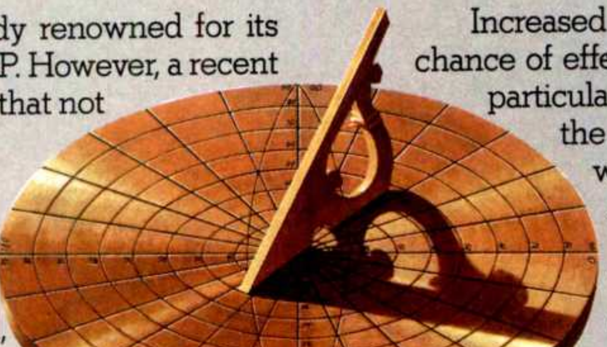

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REFERENCES
1. Sponsel, W. E., *et al., Brit. J. Ophthal.*, 1983, 67, 220.
2. Norell, S. E., *Amer. J. Ophthal.*, 1981, 92, 727.
3. MacKean, J. M., and Elkington, A. R., *Brit. J. Ophthal.*, 1983, 67, 46.
4. Reynolds, P. M., *Glaucoma*, 1982, 262.
5. Willcockson, J., and Willcockson, T., *Glaucoma*, 1982, 155.

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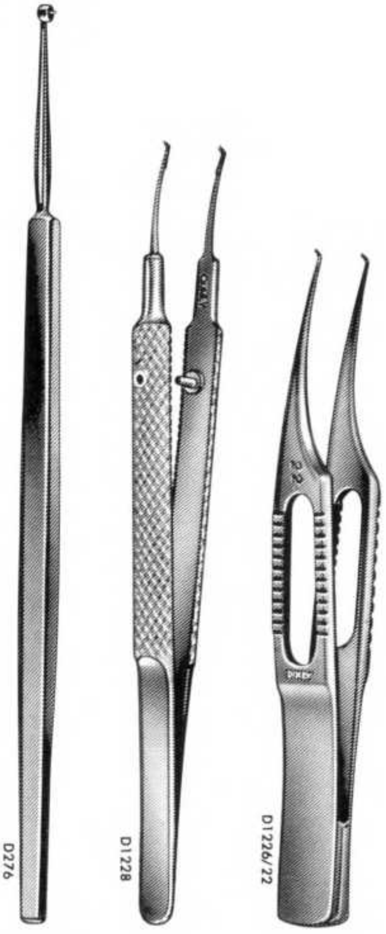

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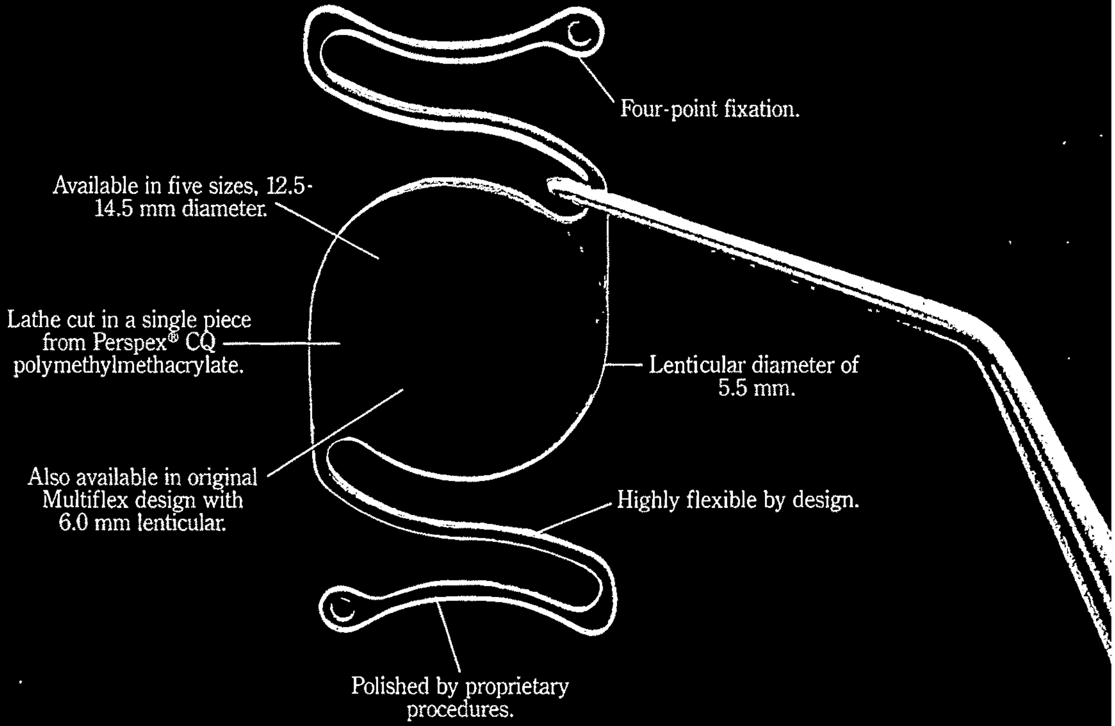
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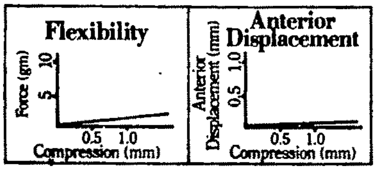

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Embolic retinopathy due to *Corynebacterium minutissimum* endocarditis

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SUMMARY Infective embolic retinopathy as a sequela of bacterial endocarditis is described in a 31-year-old woman with mitral valve prolapse. The infective organism, *Corynebacterium minutissimum*, has not been previously found to cause ocular or multisystem diseases. It is a common mucocutaneous inhabitant which causes erythrasma. In our case report both ocular involvement and septicaemia were present. The infection was confirmed by positive serial blood cultures. Mitral valve prolapse was confirmed by echocardiography. On clinical examination the retinopathy consisted of white intraretinal lesions which resolved with antibiotic therapy. By fluorescein angiography focal areas of hypofluorescence corresponding to the white fundus lesions were present. Optic disc oedema was also seen.

Corynebacterium minutissimum is a common mucocutaneous inhabitant which causes erythrasma, a mild, localised, superficial skin infection.[1 2] This communication reports an unusual case of embolic retinopathy, bacterial endocarditis, mitral valve prolapse, and septicaemia due to *C. minutissimum*. The species has not previously been implicated as the cause of ocular or multisystem infection.

Sterile emboli causing cerebral ischaemia[3] and retinal vascular occlusions[4] have been shown to have their origin from prolapsing mitral valves. In the present case vegetation on the prolapsing mitral valves is believed to be the source of the emboli.

Case report

A 31-year-old woman was admitted to the Scheie Eye Institute one day after the onset of decreased vision and photophobia of the left eye. During the preceding week she noted metamorphopsia and spots in that eye. For the last four months she had had fever and chills, frontal headaches, anorexia, weight loss, fatigue, intermittent migratory polyarthritis, and arthralgia. She had been placed on prophylactic antibiotics after rheumatic fever at the age of 7 years; this medication ceased three years prior to admission to hospital. After tubal ligation one year before admission echocardiography had shown prolapse of the mitral valve. In addition she had recently undergone dental surgery.

Visual acuity was 6/6 in each eye. Slit-lamp biomicroscopy showed 1+ flare and cells in the anterior chamber and vitreous bilaterally. Intraocular pressures were normal. Ophthalmoscopic examination of the right eye showed one white intraretinal lesion with a fine rim of haemorrhage one disc

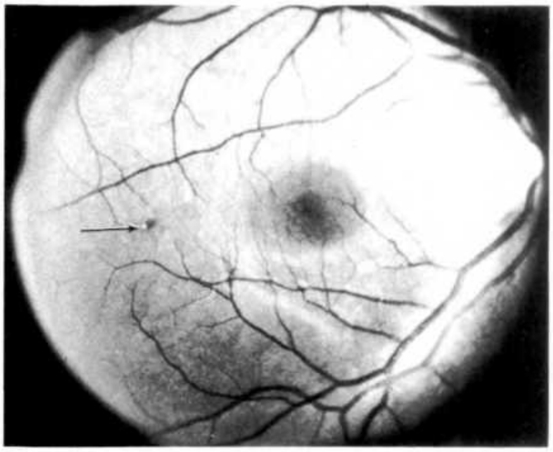

Fig. 1 *Right macula. White intraretinal lesion with rim of haemorrhage prior to therapy* (arrow).

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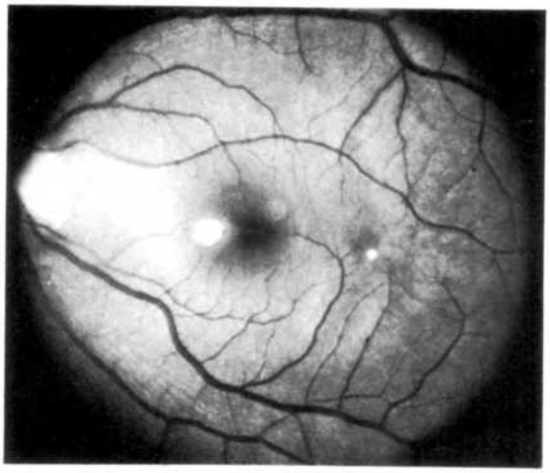

Fig. 2 *Left macula. Discrete white intraretinal lesions seen prior to therapy. (Photographic artefact superotemporal to the fovea).*

diameter temporal to the fovea (Fig. 1). A second white intraretinal lesion was seen near the ora serrata. In the left eye a white intraretinal lesion of one-fifth disc diameter was seen in the papillomacular bundle (Fig. 2). A zone of surrounding oedema extended to the nasal edge of the fovea. A second lesion was situated one and one half disc diameters temporal to the fovea (Fig. 2), with a third lesion located peripherally. Fluorescein angiography (Fig. 3) showed areas of hypofluorescence corresponding to the white lesions bilaterally. Fluorescein dye from the surrounding retinal capillaries filled these areas and showed late staining of the retina. Leakage of dye from both the optic discs consistent with papillitis was seen (Fig. 4). Cardiac auscultation revealed a grade II/VI apical, holosystolic, nonradiating murmur. The rest of the examination, including mucocutaneous tissues, was entirely normal.

Blood cultures were positive for significant exclusive growth of *Corynebacterium minutissimum*. The organism was sensitive to penicillin. Echocardiography indicated vegetations on the anterior leaflet of a prolapsing mitral valve consistent with bacterial endocarditis. Blood studies revealed a microcytic, hypochromic iron deficiency anaemia. Serum IgM and IgG were elevated at 2451 mg/dl and 672 mg/dl respectively (24·5 and 6·7 g/l).

Treatment for subacute bacterial endocarditis was initiated with 4 million units of aqueous penicillin intravenously every four hours for four weeks.

Funduscopic examination during hospital admission showed rapid resolution of the peripheral lesions, while the lesions in the posterior pole resolved slowly. Five weeks after therapy was initiated the lesion in the right fundus had disappeared and the lesions of the left fundus showed significant improvement of both clinical and fluorescein angiographic appearances.

Discussion

Corynebacterium minutissimum has not been reported previously as a cause of endophthalmitis and endocarditis. Corynebacteria are frequent inhabitants of normal skin and mucous membranes[5 6] and frequently contaminate blood cultures.[7] *C.*

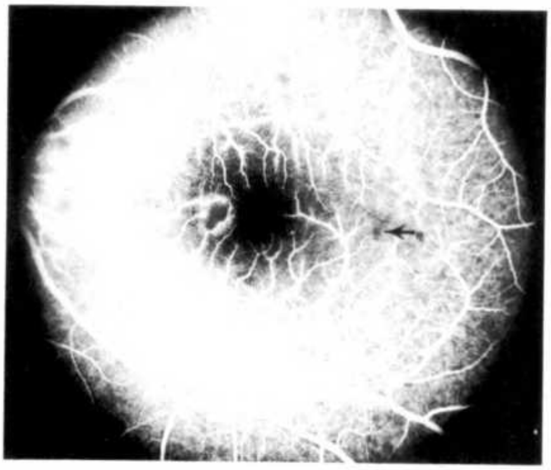

Fig. 3A *Left macula. Fluorescein angiogram prior to therapy. Midvenous phase showing area of hypofluorescence corresponding to large white lesion seen clinically (Fig. 2). Smaller lesion* (arrow) *also appears hypofluorescent.*

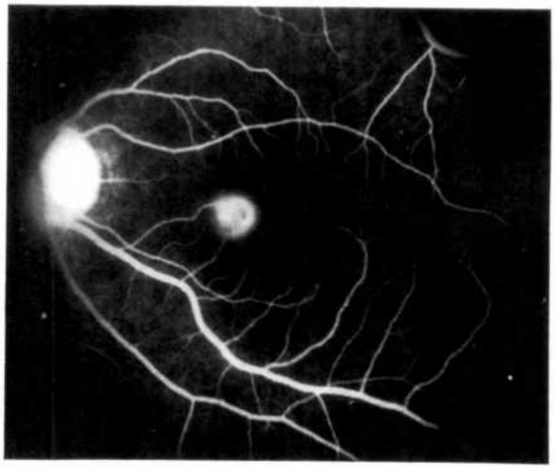

Fig. 3B *Late phase. Fluorescein dye fills area of previously described hypofluorescence. Smaller lesion is essentially inapparent.*

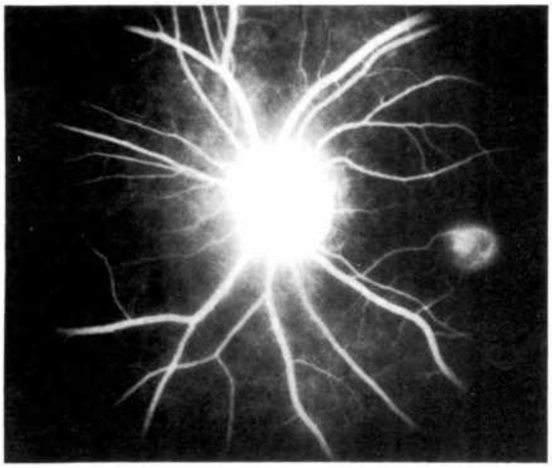

Fig. 4 *Left eye. Diffuse leakage of dye from the optic disc late in the angiogram.*

minutissimum has been considered to be systemically harmless in humans. It is responsible, however, for erythrasma, a mild, chronic, localised, superficial infection of body clefts and folds.[1] Cases of corynebacterial endocarditis constitute less than 0·3% of all cases of endocarditis[8] and usually affected prosthetic heart valves. None have been reported on an isolated prolapsing mitral valve.[6,8-11] Generally, the reported incidence of bacterial endocarditis in mitral valve prolapse is 2 to 6%.[11]

In the present case *C. minutissimum* was confirmed by serial blood cultures. The mitral valve prolapse may have served as a predisposing factor for the infection. The ocular signs consisted exclusively of multiple, intraretinal white lesions sometimes associated with a fine rim of haemorrhage. By fluorescein angiography leakage of dye into the tissue surrounding the lesions suggested an active inflammatory process. Papillitis, which was not clinically apparent, was revealed by the angiographic study. The nature of the lesions is thought to be the accumulation of the inflammatory white cells surrounding the sites of bacterial emboli.

References

1 Sarkany I, Taplin D, Blank H. The etiology and treatment of erythrasma. *J Invest Dermatol* 1961; **37:** 282–90, 801–3.

2 Hoeprich PD, ed. *Infectious diseases*, 2nd ed. Hagerstown: Harper and Row, 1977.

3 Barnett HJM, Jones MW, Boughner DR, Kostuk WJ. Cerebral ischemic events associated with prolapsing mitral valves. *Arch Neurol* 1976; **33:** 777–82.

4 Woldoff HS, Gerber M, Desser KB, Benchimol A. Retinal vascular lesions in two patients with prolapsed mitral valve leaflets. *Am J Ophthalmol* 1975; **79:** 382–5.

5 Locatcher-Khorzao D, Segal BC. *Microbiology of the eye*. St Louis: Mosby, 1972.

6 Kaplan D, Weinstein L. Diphtheroid infections of man. *Ann Intern Med* 1969; **70:** 919–29.

7 Washington JA II. Comparison of two commercially available media for detection of bacteremia. *Appl Microbiol* 1971; **22:** 604–7.

8 Reid JD, Greenwood L. Corynebacterial endocarditis. *Arch Intern Med* 1967; **119:** 106–10.

9 Blount JG. Bacterial endocarditis. *Am J Med* 1965; **38:** 909–22.

10 Gerry JL, Greenbough WB III. Diphtheroid endocarditis: report of nine cases and review of the literature. *Johns Hopkins Med J* 1976; **139:** 61–8.

11 Coker JE, Dworzack DL, Hodges GR, Petrie SC, Pugh DM. The infected mitral valve. *J Kans Med Soc* 1978; **79:** 550–2.

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An unusual case of congenital unilateral Coats's disease associated with morning glory optic disc anomaly

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SUMMARY We present the case of a 13-year-old girl with a right congenital esotropia who at the age of 6 months presented an anomaly of the optic disc and retinal vessels in the same eye. In the following year she developed Coats's disease, rubeosis iridis, and neovascular glaucoma that led to enucleation. Pathological examination confirmed the clinical diagnosis.

One of the most interesting retinal vascular diseases, the pathogenesis of which is still controversial, is Coats's disease.[1] The classical features common to this disease are: the comparatively young age of the patients, the absence of any systemic disease, the high unilateral incidence of the ocular disturbances, and the insidious onset and slow progression.[2-7] Coats's disease may be confused with retinoblastoma. Most of the histopathological data on this entity have come from enucleated eyes, especially in children under the age of 4 years.[8-10]

The embryonic fissure normally begins to close around the end of the fourth week of intrauterine life, and the closure proceeds anteriorly and posteriorly. Because the portion of the embryonic fissure in the region of the optic papilla is the last to close, isolated colobomas of the optic nerve head are not uncommon.[11-20] These may be partial or complete and may be inherited usually as an autosomal dominant trait.[20-23]

The following case presents the problems of diagnosis of Coats's disease especially when it is combined with another rare anomaly such as morning glory type of optic disc coloboma.

Case report

A 13-year-old girl was admitted to our department with a longstanding neovascular glaucoma of her right eye. She suffered from congenital esotropia in this eye and underwent stabismus operation in another hospital when she was 1-year-old. Her medical file from that hospital showed that she suffered from organic amblyopia in this eye, and its visual acuity was never more than 1/60. The abnormal findings found then were morning glory type of optic disc anomaly with gliosis of optic nerve head and peripapillary pigmentary changes, and severe degenerative changes in the inferotemporal periphery with neovascularisation in that area. There was no family history of eye diseases.

On admission the visual acuity was uncertain light projection in the right eye and 6/6 in the left one. The intraocular pressure was 40 mmHg in the right eye and 12 mmHg in the left. The right eye presented

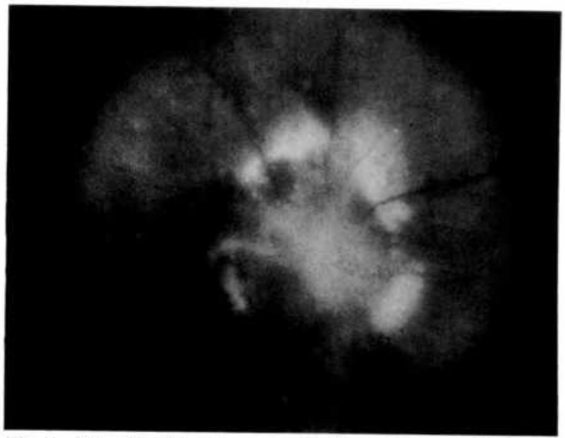

Fig. 1 *Morning glory type of optic disc coloboma with central gliotic mass.*

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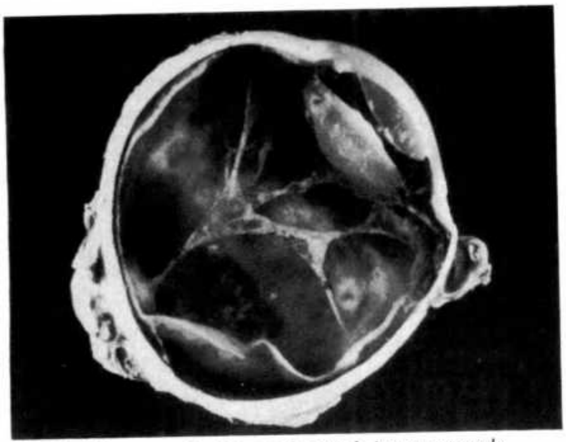

Fig. 2 *Macroscopic picture of central vitreous strands extending from the disc to the ciliary body and lens.*

ciliary and conjunctival injection, a diffuse corneal oedema with some old keratic precipitates in the endothelium, and a deep anterior chamber. Rubeosis iridis with ectropion uvea and cataractous lens were also noted. Funduscopy showed a pale disc with a big central excavation filled with a gliotic mass (Fig. 1). No central retinal artery or vein was seen, and instead there were several blood vessels leaving the disc as seen in morning glory syndrome. Perivascular sheathing was observed near the optic disc. Temporal to the macula there were confluent subretinal yellow exudates with slight raising of the sensory retina and many capillary loops. Retinal haemorrhages were found in the lower temporal quadrant.

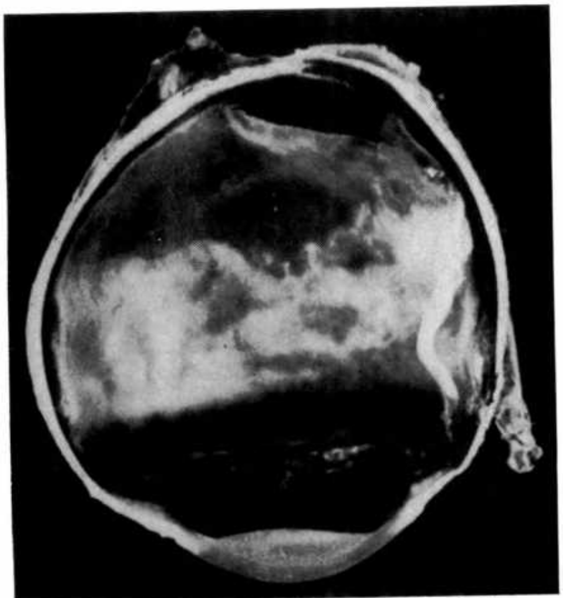

Fig. 3 *Macroscopic picture of a wide yellow band of subretinal exudation at the equatorial region.*

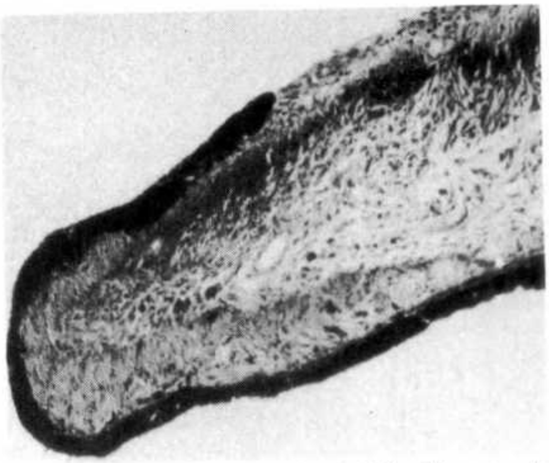

Fig. 4 *Ectropion uveae with rubeosis iridis. (Haematoxylin and eosin, × 120).*

Gonioscopy showed a closed anterior chamber angle in the right eye and an open angle in the left one. The left eye appeared normal. In spite of maximal treatment with atropine, Dexamycin (dexamethasone), timolol maleate, and Diamox (acetazolamide) the intraocular pressure did not go down, and the patient underwent cyclocryotherapy in two sessions. This treatment did not lower the pressure either and, because the patient suffered from severe pain, we decided to enucleate the right eye. In order to rule out cerebral vascular malformations the patient underwent computerised axial tomography (CT) scanning of the skull, which was normal.

Pathological examination. The dimensions of the eyeball were 24 × 21 × 21 mm and it was hard on palpation. There was a limbal depression in the lower nasal quadrant, the cornea looked clear, the anterior chamber deep, and the lens cataractous. Horizontal section was done, and fluid vitreous came out. Central vitreous strands extended from the optic disc to the ciliary body (Fig. 2). An 8 mm wide yellow band, slightly raised, was seen at the equatorial region extending to the ora serrata. Inferiorly it extended towards the macular area (Fig. 3). The optic disc appeared as a white raised mass. The macula was not clearly seen.

Microscopy. The corneal epithelium looked flat. A peripheral pannus was found, and the endothelial cells were vacuolated. In the iris there was ectropion uveae with a thick fibrovascular membrane on the anterior face (Fig. 4). Peripheral anterior synechiae were present all around. The ciliary body was atrophic, and a thick cyclitic membrane was seen in

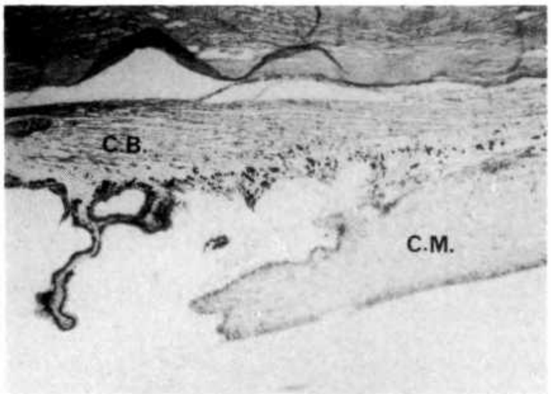

Fig. 5 *A thick cyclitic mebrane adherent to posterior half of ciliary body (Haematoxylin and eosin,* × *53).* CB = *ciliary body.* CM = *cyclitic membrane.*

its posterior half (Fig. 5). The choroid looked normal except for a marked congestion of its blood vessels.

Temporally the retina was detached with conglomerates of lipid laden macrophages in the subretinal fluid and in the external retinal layers (Fig. 6). On the same side of the retinal detachment the retina was thickened by glial proliferation associated with many thick walled and tortuous vessels. Some of them were obstructed by a hyaline material (Fig. 7). Posterior to this vascular anomaly the retina was covered internally by a thick fibrovascular membrane causing fixed folds. Temporally the retina was markedly vacuolated and atrophic. In other areas the detached retina showed a moderate atrophy with no vascular pathology. At the region of the optic disc the retina together with the retinal pigment epithelium (RPE) penetrated deep into the excavation of the disc (Fig. 8) and filled the excavation, at the centre of which some retinal vessels were visible (Fig. 9). At the border of the excavation the RPE cells showed hyperplasia and formed a thick metaplastic connec-

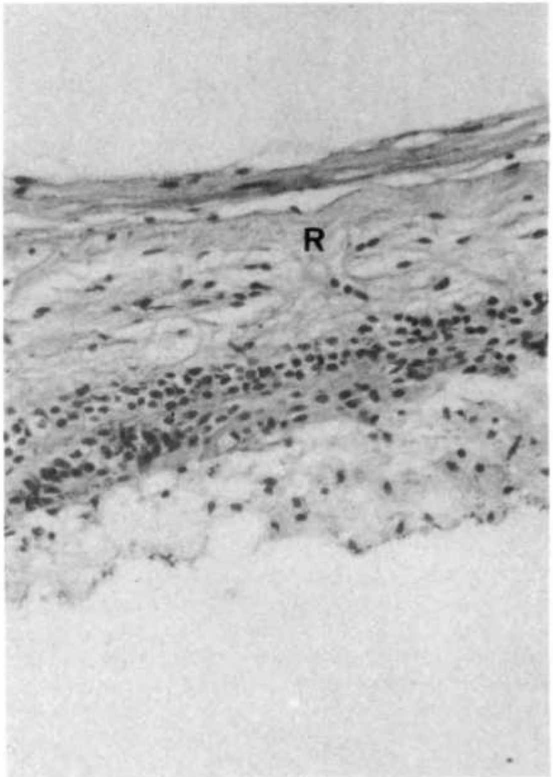

Fig. 6 *Detached retina with lipid laden macrophages mainly in subretinal space. (Haematoxylin and eosin,* × *240).*

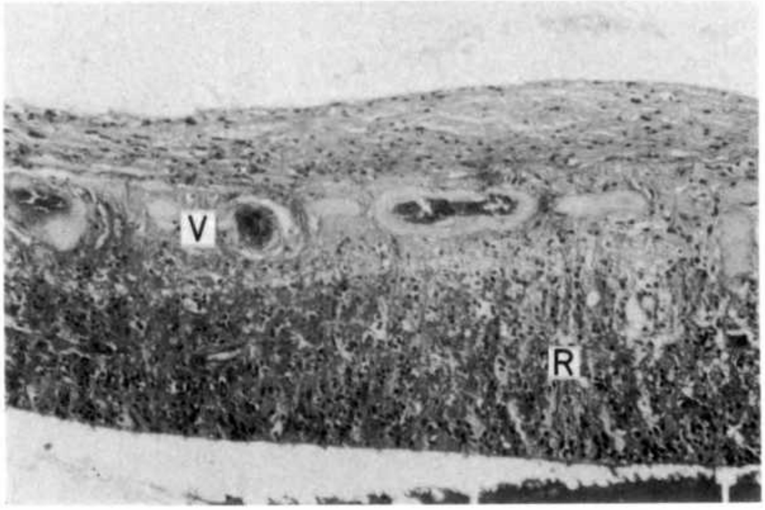

Fig. 7 *Thickened detached retina* R *with glial proliferation, thick walled vessels* V, *and preretinal fibrosis (Haematoxylin and eosin,* × *185).*

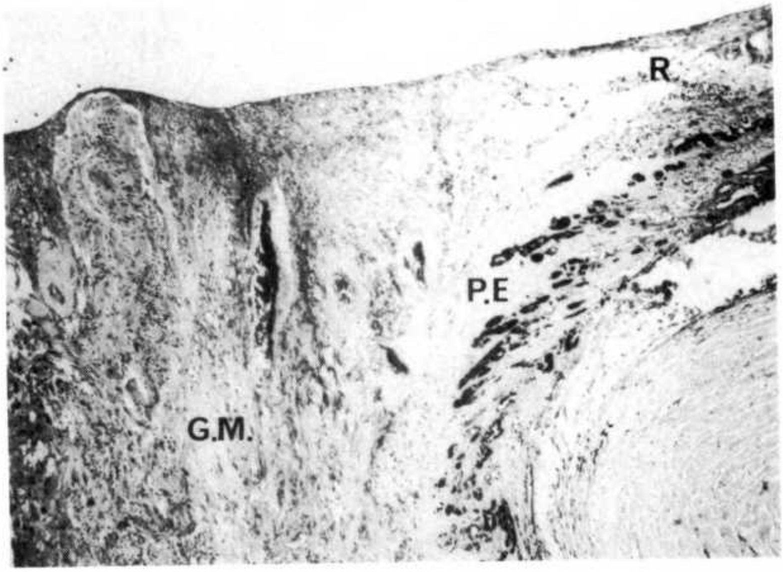

Fig. 8 *The retina together with retinal pigment epithelium (RPE) are penetrating into the periphery of the disc excavation. A large gliotic mass is seen in the centre.* R = *retina. PE=pigment epithelium* GM = *gliotic mass. (Haematoxylin and eosin,* × *46).*

tive tissue (Fig. 10). Thick walled vessels from the optic disc excavation extended into the peripapillary retina.

Discussion

Coats's disease is characterised clinically by sheets of subretinal exudation and foci of irregularly dilated capillaries, large microaneurysms, and bizarre configurations of dilated vascular channels. Subretinal haemorrhage, sometimes extensive, is mixed with exudation. Mounds of detached retina solidly raised by massive subretinal fatty exudation and haemorrhage may develop at different stages of the disease.[24-25] The disease may reach a certain stage and spontaneously regress with retinal and subretinal neovascular fibrosis with fixed retinal folds, or it may proceed to rubeosis iridis, neovascular glaucoma, and eventual loss of the eye,[25] as happened in our case. The primary lesion is thought to be abnormal permeability of the retinal vessels. The vessel walls are badly damaged which causes aneurysmic dilatation, transudation of serum with lipids, haemorrhages and occlusion of blood vessels, mainly

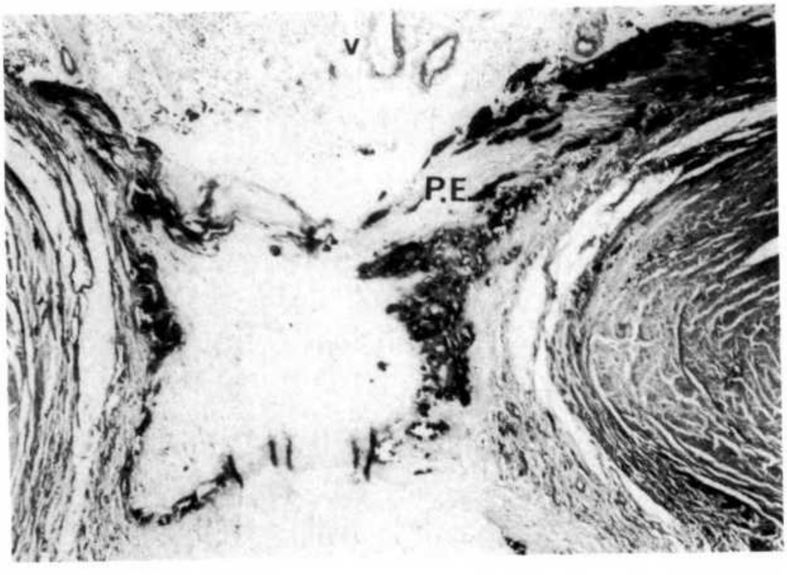

Fig. 9 *Proliferating RPE cells penetrate deep into the excavation of the optic disc. Some retinal vessels* V *are seen.* PE = *pigment epithelial cells. (Haematoxylin and eosin,* × *80).*

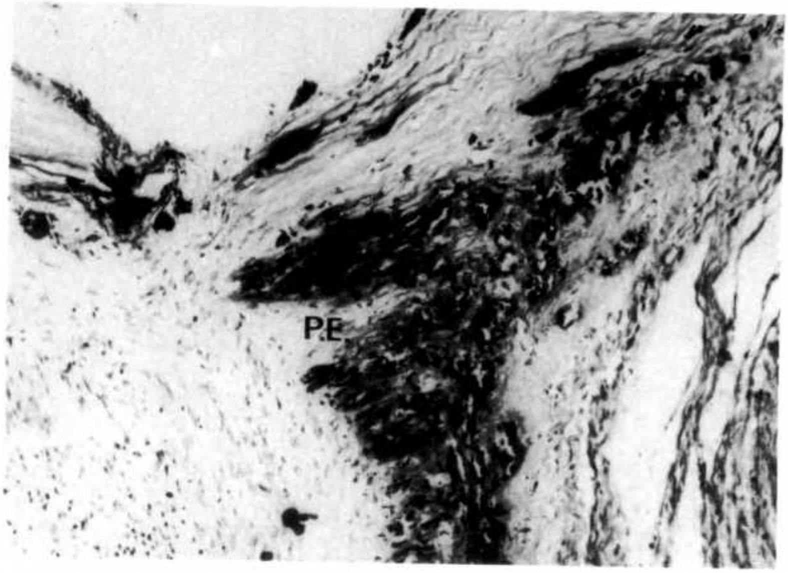

Fig. 10 *At the border of the excavation the RPE cells* PE *form a thick metaplastic connective tissue (Haematoxylin and eosin, × 111).*

peripherally. Subretinally there are massive periodic acid Schiff—(PAS)—positive fatty exudation, lipid-laden ('foamy') macrophages, cholesterol crystals, and red blood cells.[26-27] The origin of the 'foamy' macrophages is not clear. They probably arise from retinal macrophages and, doubtfully, from retinal pigment epithelial cells.[28] Coloboma of the nerve head is a congenital defect that may show as a cavity confined to the disc, or the cavity may also be present in the line of the cleft below the disc. There is apparently no sharp dividing line between cases of coloboma of the nerve head and crater-like holes in the disc. Cogan[19] and François[14] have shown that the affected part of the disc, usually the lower, is replaced by a large mass of incompletely organised tissue containing retinal and mesodermal elements. It resembles a fold of retina which has been pushed back into the lower part of the sclerochoroidal foramen causing distortion of the nerve head. Calhoun[21] described a histopathological case that was similar to the picture described in our case, in which a hole in the disc communciated with an extensive cavity containing retinal elements and passing between sclera and the optic nerve sheath.

In the above case we have found a combination of Coats's disease as a retinal vascular anomaly and optic disc coloboma associated with abnormality of the main blood vessels arrangement at the disc, as seen in morning glory syndrome. We wonder if there is any correlation between these two vascular anomalies, Coats's disease being mainly peripheral and morning glory syndrome being central. To the best of our knowledge there is no record of a similar case combining these two rare anomalies, and therefore we decided to describe this very rare and most probably coincidental association.

References

1 Coats G. Forms of retinal disease with massive exudation. *R London Ophthalmic Hosp Rep* 1908; **17:** 440-525.

2 Coats G. Über retinitis exudativa (Retinitis haemorrhagica externa). *Albrecht von Graefes Arch Klin Ophthalmol* 1912; **81:** 275–327.

3 Woods AC, Duke JR. Observations on Coats' disease. *Trans Ophthalmol Soc UK* 1962; **82:** 105-21.

4 Egerer I, Tasman W, Tomer TL. Coats' disease. *Arch Ophthalmol* 1974; **92:** 109-12.

5 Fox KR. Coats' disease. *Metab Pediatr Ophthalmol* 1980; **4:** 121-4.

6 Reese AB. Telangiectasis of the retina and Coats' disease. *Am J Ophthalmol* 1956; **42:** 1-8.

7 Harris GS. Coats' disease, diagnosis and treatment. *Can J Ophthalmol* 1970; **5:** 311-20.

8 Marshall J, Michaelson IC. Exudative retinitis in childhood. *Trans Ophthalmol Soc UK* 1933; **53:** 102-18.

9 Wise GN, Horava A. Coats' disease. *Am J Ophthalmol* 1963; **56:** 17-23.

10 Sugar HS. Coats' disease: telangiectatic or multiple vascular origin? *Am J Ophthalmol* 1958; **45:** 508-17.

11 Kindler P. Morning glory syndrome: unusual congenital optic disc anomaly. *Am J Ophthalmol* 1970; **69:** 376-84.

12 Gruner HJ, Fechner PU. Über das Morning Glory Syndrom. *Klin Monatsbl Augenheilkd* 1978; **172:** 114-5.

13 Krause U. Three cases of the morning glory syndrome. *Acta Ophthalmol (Kbh)* 1972; **50:** 188-98.

14 François J. Colobome partiel du nerf optique. *Bull Soc Belge Ophthalmol* 1964; **138:** 548-51.

15 Savell J, Cook JR. Optic nerve colobomas of autosomal-dominant heredity. *Arch Ophthalmol* 1976; **94:** 395-400.

16 Jensen PE, Kalina RE. Congenital anomalies of the optic disc. *Am J Ophthalmol* 1976; **82:** 27-31.

17 Duke Elder S, Cook C. Embryology. In: Duke Elder S. ed. *System of ophthalmology*. London: Kimpton, 1963; **3**(1): 38-40.

18 Pedler C. Unusual Coloboma of the optic nerve entrance. *Br J Ophthalmol* 1961; **45:** 803-7.

19 Cogan DG. Coloboma of optic nerve with overlay of peripapillary retina. *Br J Ophthalmol* 1978; **62:** 347-50.

20 Hughes HL. Case of bilateral Coloboma of optic disc. *Br J Ophthalmol* 1947; **31:** 689-92.

21 Calhoun FP. Bilateral coloboma of optic nerve associated with holes in disc and cyst of optic sheath. *Arch Ophthalmol* 1930; **3:** 71-9.

22 Bikle CE, Levitt JM. Coloboma of optic nerve. *Am J Ophthalmol* 1949; **32:** 700-2.

23 Payne BF. Coloboma of optic nerve in human embryo *Am J Ophthalmol* 1941; **24:** 395-402.

24 Farkas TG, Potts AM, Boone C. Some pathologic and biochemical aspects of Coats' disease. *Am J Ophthalmol* 1973; **75:** 289-301.

25 Meythaler H. Zur pathologischen anatomie der retinitis exsudativa externa. *Klin Monatsbl Augenheilkd* 1970; **156:** 644.

26 Tripathi R, Ashton N. Electron microscopical study of Coats' disease. *Br J Ophthalmol* 1971; **55:** 289-301.

27 Manschot WA, Brüijn WC de. Coats' disease: definition and pathogenesis. *Br J Ophthalmol* 1967; **51:** 145-57.

28 Takei Y. Origin of ghost cell in Coats' disease. *Invest Ophthalmol Visual Sci* 1976; **15:** 677-81.

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Effect of orally administered nadolol on the intraocular pressure in normal volunteers

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SUMMARY Forty six normal volunteers were randomly assigned in double-blind fashion to once daily orally administered nadolol 10, 20, 40, or 80 mg for five days. Significant and dose related intraocular pressure (IOP) reductions (range 20–40%) were demonstrated both at three hours and 24 hours post dosing ($p<0{\cdot}001$, all dosages). The reductions in IOP were dose related ($p<0{\cdot}05$). One subject (in the 10 mg group) failed to show a significant intraocular pressure reduction. Significant reductions in blood pressure and heart rate also were recorded at all dose levels (with the exception of diastolic pressure in the 10 mg group), though considerably less in degree than IOP reductions. Two subjects (20 mg and 80 mg groups) experienced known side effects of β blocker therapy necessitating termination of the drug, and four others experienced mild side effects but had no difficulty completing the study. The results have prompted further investigation of the usefulness of low doses of oral nadolol as therapy in chronic simple glaucoma patients.

Since 1967 when Phillips *et al.* first demonstrated the ocular hypotensive effect of propranolol,[1] it has been shown that most β blockers, given either topically or systemically, can lower intraocular pressure (IOP) to varying degrees in either normal or glaucomatous eyes.[2] The mechanism of action is not clear, but blockade of the β receptors in the ciliary body appears to decrease aqueous inflow.[3] Recent work (J. Williamson) indicates that these receptors are mostly of the β 2 type, which might explain why the IOP lowering action of propranolol and timolol (non-selective blockade) is maintained in the long term, whereas the action of atenolol (β 1 blockade) appears to wane during chronic administration.[4]

Nadolol is a non-selective β blocking agent with the longest half life of this class of compound (20–24 hours) and thus is suitable for once daily administration.[5] This study was designed to determine the degree and duration of the ocular hypotensive effect of four dose strengths of oral nadolol (10, 20, 40, and 80 mg) in normal volunteers with a view to ascertaining whether, and at what doses, once daily nadolol administration might be useful in the treatment of glaucoma. In view of the increasing number of patients on chronic β blocker therapy for a variety of reasons—including, in our experience, many in the glaucoma clinic population—the results might have clinical implications.

Materials and methods

Subjects. A group of 46 normal adult volunteers (32 men, 14 women), mean age 25 years (range 19 to 58), participated in this study. Prior to entry all subjects underwent a general physical examination and had intraocular pressures in each eye recorded by Goldmann applanation tonometry. Subjects were excluded for the following reasons: pretreatment hypertension (diastolic pressure >90 mmHg, systolic pressure >140 mmHg); raised pretreatment IOP (>21 mmHg in either eye); history of heart disease, asthma, or bronchospasm; impaired renal or hepatic function; receiving other medication that could affect IOP; pregnancy or women of childbearing age not practising adequate methods of contraception. All subjects were made fully aware of the conditions and drugs used in the study and provided informed consent. The study protocol was approved by the hospital's Ethics Committee.

Procedure. The active treatment phase of this study was conducted in double-blind fashion. The 46 subjects satisfying the criteria for entry were randomised into four treatment groups one group for each of the four nadolol dose levels studied (10, 20, 40, and 80 mg daily). Each treatment group progressed through four periods as follows:

Day 0–7	Day 8–12	Day 13–15	Day 16–22
Placebo	Nadolol	Nadolol step down	Placebo

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The investigators were aware of placebo and nadolol periods but not of nadolol potencies. (Double-blind supplies of nadolol and matching placebo were made available by the manufacturer, E. R. Squibb and Sons Ltd.)

Following the initial assessment and enrolment visits were made on days 3 and 7 of the pretreatment placebo period, days 8 through 12 (active treatment), day 15 (completion of dosage step down), and days 16 through 22 (post-treatment placebo period). Visits were timed to occur approximately three hours after the morning dose of medication except for one visit on either day 10 or 11 during active treatment, when the visit was timed to take place 23 to 24 hours following the previous day's dose.

At each visit IOP was measured by Goldmann applanation tonometry, and blood pressure and pulse rate were recorded after five minutes in the supine position. One person was responsible for both tonometric and vital sign measurements throughout the study. Measurements recorded on days three and seven were averaged and considered as baseline values. On day seven, and at the end of the full nadolol dosage period (day 12), the following further measurements were made: visual acuity, amplitude of accommodation, pupil diameter, and refraction.

During the nadolol dosage step down period the dosage of the 40 and 80 mg groups was halved. The dosage of subjects receiving 10 and 20 mg daily continued unchanged.

Results

Forty two of the 46 subjects completed the 22-day study. One subject withdrew during the placebo period for personal reasons. Three others withdrew towards the end of the treatment period because of side effects (2) and concomitant illness (1) but provided data suitable for evaluation.

The IOP lowering effect of the four dose strengths of nadolol is shown in Table 1. The average for both eyes of all IOP measurements taken three hours after the dose (excluding the first nadolol dose, that is day 8) shows a mean percentage IOP reduction from baseline of 29·5, 36·4, 36·9, and 41·0% with the 10, 20, 40, and 80 mg doses respectively ($p<0·001$ for each dose level). Only one subject in the trial (10 mg group) failed to show a significant IOP reduction. The log dose response when adjusted for baseline differences demonstrated that pressure reductions were significantly dose related ($p<0·05$).

Large and statistically significant pressure reductions also were demonstrated 23–24 hours after dosing (Table 2). These were respectively 21·1, 22·2, 30·0, and 39·7% with the 10, 20, 40, and 80 mg doses ($p<0·001$ for each dose level). The attenuation of the hypotensive response at 23–24 hours was statistically significant in the 10 and 20 mg groups ($p<0·05$ and $p<0·01$ respectively).

Reductions in systolic pressure, diastolic pressure, and pulse rate ranged from 5 to 11%, 4 to 11%, and 17 to 20% respectively. With the exception of the diastolic pressure in the 10 mg group these reductions were statistically significant at all dose levels (range $p<0·05–<0·001$), and, in the case of systolic and diastolic pressure, showed a significant dose response relationship ($p<0·05$). The relative effects on the eye and the cardiovascular system are shown graphically in Fig. 1. Reductions in IOP were twice those of heart rate and more than three times those of systolic and diastolic blood pressure. In all four dosage groups both vital signs and IOP returned to baseline levels during the final placebo period.

Two subjects (4·4%) were discontinued because of

Table 1 *Mean IOP change from baseline three hours post dose among normal subjects receiving different doses of oral nadolol: results averaged over three treatment days*

Dose mg	*n*	*Baseline IOP mmHg*	*Treatment IOP mmHg*	*IOP reduction mmHg*	*% IOP reduction*	*p value*
10	12	15·6	11·0	4·6	29·5	<0·001
20	11	16·2	10·3	5·9	36·4	<0·001
40	11	15·7	9·9	5·8	36·9	<0·001
80	11	15·6	9·2	6·4	41·0	<0·001

Table 2 *Mean IOP change from baseline 23–24 hours post dose among normal subjects receiving different doses of oral nadolol: results obtained at one visit after at least three days active therapy*

Dose mg	*n*	*Baseline IOP mmHg*	*Treatment IOP mmHg*	*IOP reduction mmHg*	*% IOP reduction*	*p value*
10	11	15·6	12·3	3·3	21·1	<0·001
20	10	16·2	12·6	3·6	22·2	<0·001
40	11	15·7	11·0	4·7	30·0	<0·001
80	10	15·6	9·4	6·2	39·7	<0·001

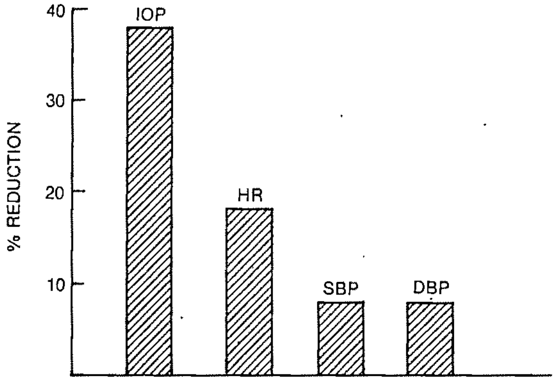


Fig. 1 *Relative reductions in intraocular pressure (IOP), systolic pressure (SBP), diastolic pressure (DBP), and heart rate (HR) for all doses combined.*

side effects associated with β blockade. One, a 45-year-old man receiving 20 mg, developed bradycardia (42 beats per minute); the other, a 48-year-old woman in the 80 mg group, experienced breathlessness, tiredness, and dry mouth. Mild side effects were reported by a further four subjects (8·9%): two cases of fatigue (20 and 80 mg groups), one case of slight nausea (20 mg group), and one episode of dizziness in a subject in the 40 mg group.

Oral nadolol treatment had no effect on the ocular parameters of visual acuity, accommodation, pupil size, and refraction.

Discussion

The ocular hypotensive effect of orally administered nadolol in normal subjects at all dose levels employed in this study was considerable, even after 24 hours. The IOP reductions observed with low to modest doses of nadolol appear to be of greater magnitude than those previously reported in normal volunteers following the oral use of both atenolol and propranolol in corresponding, and higher, doses.[6 7]

Oral nadolol was well tolerated with only two patients (4·4%) being discontinued for side effects common to β blockers. The pulse rate reductions of 17–20% were impressive, but even with topical timolol administered twice daily to both eyes pulse rate reductions approximating 14% may be experienced.[8]

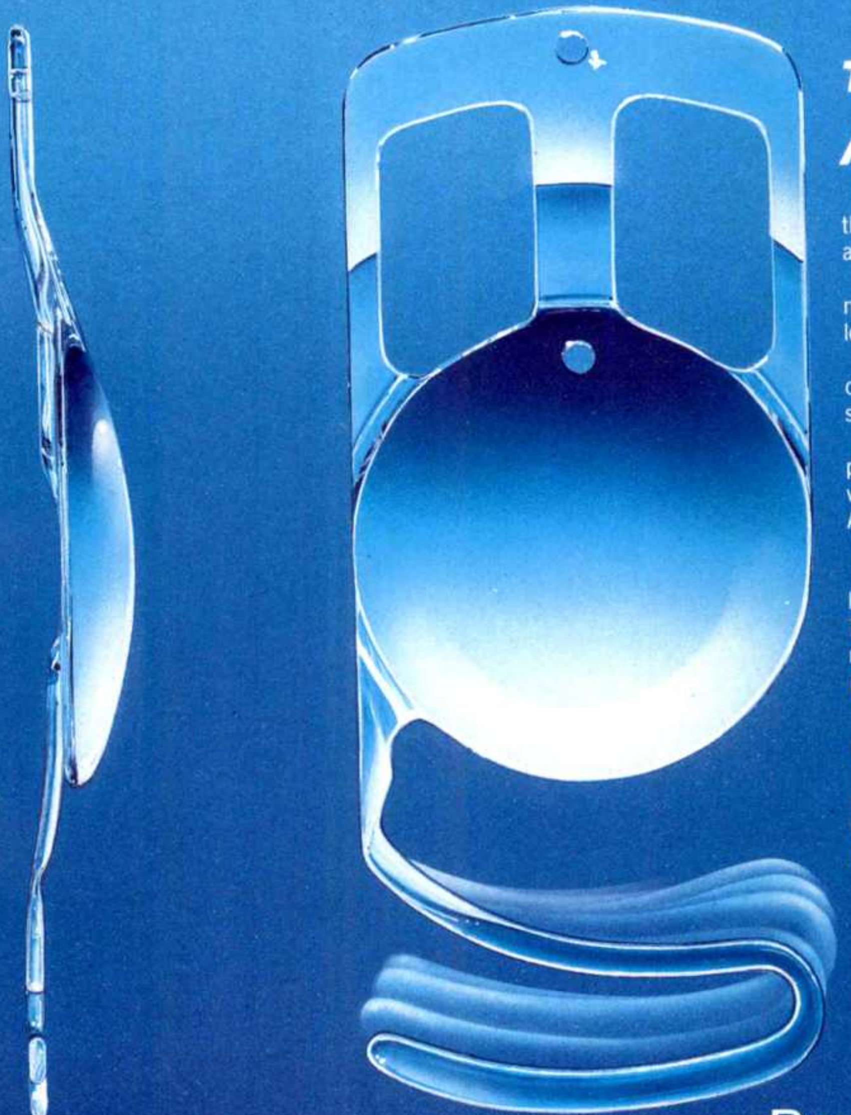
Our results indicate that 20 and 40 mg once daily oral doses of nadolol (less than the usual starting dose of 80 mg in hypertension) may have a therapeutic role in the management of glaucoma. Furthermore an increasing number of patients—including, in our experience, a growing percentage of those in the glaucoma clinic population—already are receiving oral β blockers for cardiovascular indications. Thus there is a subset of glaucoma patients who present the possibility of having their β blocker therapy rationalised to treat two diseases.

From our results in normal subjects we decided to study the use of once daily oral nadolol in patients with chronic simple glaucoma.[9]

References

1 Phillips CI, Howitt G, Rowlands DJ. Propranolol as ocular hypotensive agent. *Br J Ophthalmol* 1967; **51:** 222–6.
2 Wettrell K, Pandolfi M. Beta-adrenoceptor blocking agents in the management of glaucoma. In: Bellow JG, ed. *Glaucoma manual.* New York: Masson, 1979; 367–75.
3 Thomas JV, Epstein DL. Timolol and epinephrine in primary open-angle glaucoma. *Arch Ophthalmol* 1971; **99:** 91–5.
4 Brenkman RF. Long-term hypotensive effect of atenolol 4% eyedrops. *Br J Ophthalmol* 1978; **62:** 287–91.
5 Frishman W. Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 9. Nadolol: a new long-acting beta-adrenoceptor blocking drug. *Am Heart J* 1980; **99:** 124–8.
6 Wettrell K, Pandolfi M. Effect of oral administration of various beta-blocking agents on the intraocular pressure in healthy volunteers. *Exp Eye Res* 1975; **21:** 451–6.
7 Ohrstrom A, Pandolfi M. Regulation of intraocular pressure and pupil size by β-blockers and epinephrine. *Arch Ophthalmol* 1980; **98:** 2182–4.
8 Boger WP, Puliafito CA, Steinert RF, Langston DP. Long-term experience with timolol ophthalmic solution in patients with open-angle glaucoma. *Ophthalmology* 1978; **85:** 259–67.
9 Williamson J, Young JDH, Atta H, Muir G, Kadom H. Comparative efficacy of orally and topically administered β blockers for chronic simple glaucoma. *Br J Ophthalmol* 1985; **69:** 41–5.

Precisely



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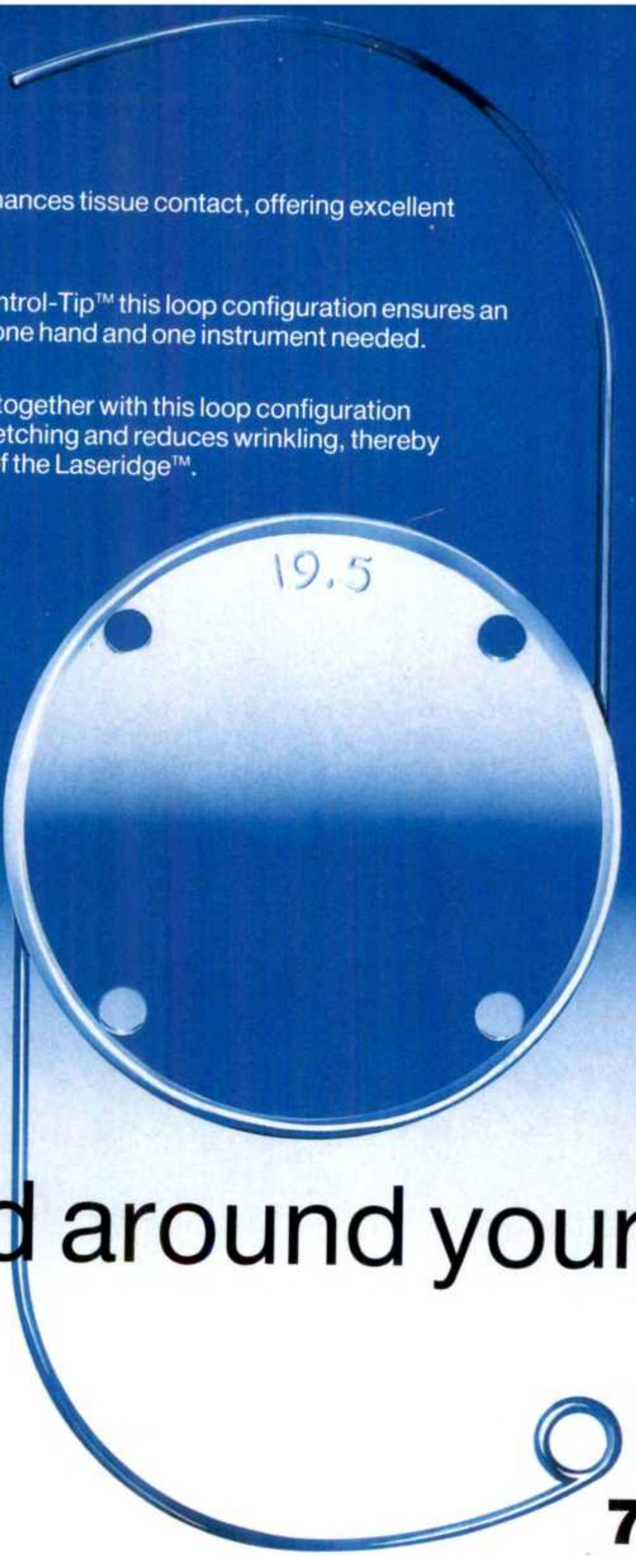

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Comparative efficacy of orally and topically administered β blockers for chronic simple glaucoma

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SUMMARY This open study of β blockers in chronic simple glaucoma compared the efficacy of once daily (o.d.) oral nadolol therapy with twice daily (b.d.) topical timolol therapy. Sixty eight patients were randomly assigned to starting doses of either 20, 40, or 80 mg of nadolol o.d. (51 patients) or 0·25% timolol b.d. (17 patients) and were seen at weekly intervals for a four-week (short-term) period. Upward dosage titration (80 mg o.d. maximum, nadolol and 0·5% b.d. maximum, timolol) was permitted if, at any visit, the intraocular pressure (IOP) in either eye was greater than 21 mmHg. At the end of 4 weeks the IOPs of a comparable number of patients were controlled (IOP<22 mmHg) with 20 mg nadolol o.d. and 0·25% timolol b.d. The 40 mg and 80 mg o.d. nadolol regimens were comparable with each other, superior to the 20 mg regimen, and (at least) equivalent to 0·5% timolol. The absolute degree of IOP reduction achieved with oral nadolol was equivalent to that with topical timolol. Alterations in blood pressure and heart rate were predictably greater with the orally administered β blocker. Long-term therapy (up to 24 months) in 28 nadolol patients and 5 timolol patients indicates no more likelihood of tolerance with nadolol therapy. Patient withdrawals from the study due to adverse reactions occurred with nadolol but not timolol. Since oral nadolol administered once daily is as efficacious as b.d. topical timolol, it can be recommended as first-line therapy for certain subsets of the glaucoma clinic population.

The results of a double-blind study of the ocular hypotensive effect of low oral doses of nadolol (10, 20, 40, and 80 mg, once daily) in normal volunteers are reported.[1] Considerable dose related reductions (30% to 40%) of intraocular pressure (IOP) were obtained and were maintained for 24 hours with the 40 mg and 80 mg doses. There was a slight loss of effect after this time interval with the two lower doses, but reductions 20% or more were preserved. Previously published reports of the ocular hypotensive effect in normal subjects of oral propranolol and atenolol at corresponding or higher doses (40 mg b.d. and 50 mg b.d., respectively) showed IOP reductions of up to 25%.[2,3] Thus, in view of what was considered to be an excellent IOP lowering potential of even low doses of nadolol, we have compared the efficacy of three regimens of once daily oral nadolol (20, 40, and 80 mg) with the two standard twice daily regimens of topical timolol (0·25% and 0·5%) in patients with chronic simple glaucoma.

A further consideration in undertaking this study has been the growing awareness in recent years that an increasing number of patients in our glaucoma clinic population are receiving oral β blockers for a variety of conditions. If β blockers, so administered, can reduce IOP to acceptable levels during chronic administration, then there is clearly a justification for rationalisation of therapy in these patients in the interests of good practice and safety, if not economy.

Material and methods

SUBJECTS

This was an open study conducted at two centres to compare the efficacy of three regimens of once daily, orally administered, nadolol (20, 40, and 80 mg) with that of twice daily, topically administered, timolol (0·25% and 0·5%) in the treatment of chronic simple glaucoma. Sixty eight patients (32 men and 36 women), mean age 59 years (range 29-81), were randomised to begin treatment with one of the three nadolol dosages o.d. (n=51) or with a starting dose of

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0·25% timolol b.d. (n=17). Patients were considered to have chronic simple glaucoma if their IOPs when not taking medication were greater than 21 mmHg by Goldmann applanation tonometry, and if there was coexisting characteristic abnormality in their visual fields or optic nerve heads or both. Exclusion criteria were as described for the normal volunteers' study,[1] and in addition patients were ineligible if there was electrocardiographic (ECG) evidence of defective cardiac conduction or left ventricular hypertrophy. Written informed consent was obtained from all subjects, and the study protocol was approved by the ethics committee in each centre.

PROCEDURE

After a general physical examination and ECG screening eligible patients entered a one- to four-week washout period, during which no glaucoma medication was prescribed. When the IOP in both eyes rose above 21 mmHg patients were randomised to one of four initial treatment groups: once daily nadolol 20, 40, or 80 mg; or 0·25% timolol, one drop to each eye b.d. The study design was as follows:

1–4 Weeks	→	4 Weeks	→	Up to 2 years
washout		short-term		long-term

Short-term. At the beginning of the short-term portion of the study the following baseline measurements were recorded: Goldmann applanation tonometry; pulse and blood pressure readings (after 5 min supine); visual acuity; accommodation; pupillometry; refraction; and Schirmer tear test. In addition the visual fields of both eyes of patients in the nadolol treatment groups were charted. At each weekly short-term visit patients returned approximately three to six hours after their morning medication for measurement of IOP, heart rate, and blood pressure. At the final short-term visit (4 weeks) measurements of the additional ocular parameters (except fields) were again taken. At any visit during short-term, if the IOP in either eye was greater than 21 mmHg, patients in the nadolol 20 mg or 40 mg treatment groups could have their dosage doubled, and patients receiving 0·25% timolol b.d. could switch to 0·5% b.d. However, the maximum dose of nadolol allowed was 80 mg once daily and of timolol 0·5% b.d. An additional visit during the final week of short-term therapy permitted IOP measurements to be made 23-24 hours after the previous morning's dose of nadolol and 11-12 hours after the previous evening's dose of timolol.

Long-term. Patients treated successfully with nadolol during short-term (IOP<22 mmHg, both eyes) were asked to continue the drug for long-term monitoring. During this long-term period IOPs, blood pressures, and heart rates were measured at monthly intervals with the same upward dosage titration provision as before. The additional ocular measurements (including fields) taken at the baseline visit was repeated at four-monthly intervals. The study protocol did not call for the long-term follow-up of timolol treated patients but, in the event, one of us (JW) did follow up a limited number of patients.

Statistical comparisons. Baseline characteristics of patients were compared by one way analysis of variance and Duncan's multiple range test. Changes in IOP were compared (where applicable) by one way analysis of covariance, which adjusts for pretreatment differences.

Results

IOP CONTROL—SHORT-TERM

All 68 patients randomised to treatment groups provided data suitable for evaluation. There were no statistically significant differences among the four initial treatment groups in terms of baseline IOPs, duration of prior glaucoma therapy, or numbers of patients previously requiring multiple drug therapy. The mean age of patients randomised to 20 mg nadolol was, however, less than that of patients initially assigned to the 40 mg dose (p<0·05).

The clinical course of patients during four weeks of short-term therapy is shown in Fig. 1. Forty (78%) of the nadolol treated patients were controlled (IOP

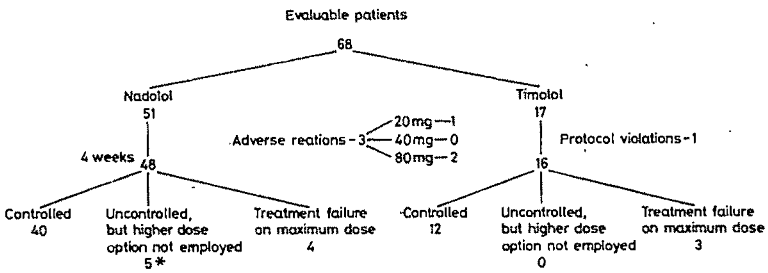
Evaluable patients
68
Nadolol
51
Timolol
17
Adverse reactions - 3
20mg — 1
40mg — 0
80mg — 2
Protocol violations - 1
4 weeks
48
16
Controlled
40
Uncontrolled, but higher dose option not employed
5*
Treatment failure on maximum dose
4
Controlled
12
Uncontrolled, but higher dose option not employed
0
Treatment failure on maximum dose
3

Fig. 1 *The clinical course of patients during four weeks of short term therapy.*

* Two of these patients continued into long-term therapy. One subsequently achieved control at the same dose (40mg.) and one achieved control after doubling dose to 40mg.

Table 1 *Distribution of patients by treatment group and dose at each visit*

Initial dose group	*Week 1*	*Week 2*	*Week 3*	*Week 4*	*Last short term**
	No of patients				
Nadolol 20 mg (n=17)					
20 mg	17	14	10	10	10
40 mg	0	3	6	5	6
80 mg	0	0	0	1	1
Nadolol 40 mg (n=18)					
40 mg	18	18	17	17	17
80 mg	0	0	1	1	1
Nadolol 80 mg (n=16)					
80 mg	16	16	14	13†	15†
Timolol 0·25% (n=17)					
0·25%	17	9	9	9	10
0·5%	0	7	6	4	7

*One, two, and four patients dropped out of the nadolol 20 mg, 80 mg; and timolol 0·25% groups prior to week four.
†Dosage was reduced to 40 mg in one patient.

Table 2 *Effect of nadolol on IOP: short-term therapy (four weeks)*

Initial dose group	*n*		*Final daily dosage*		
			Nadolol 20 mg	*Nadolol 40 mg*	*Nadolol 80 mg*
Nadolol 20 mg	17	Controlled*	7	4	1
		Uncontrolled	3	1	0
		D/C, ADR	0	1	0
Nadolol 40 mg	18	Controlled*	0	16	1
		Uncontrolled	0	1	0
		D/C, ADR	0	0	0
Nadolol 80 mg	16	Controlled*	0	1	10
		Uncontrolled	0	0	3
		D/C, ADR	0	2	0

D/C=Discontinued.
ADR=Adverse reaction.
*IOP less than 22 mmHg (both eyes).

Table 3 *Short-term outcome by initial and final timolol dosage*

Initial dose group	*n*		*Final dosage (b.d.)*	
			Timolol 0·25%	*Timolol 0·5%*
Timolol 0·25%	17	Controlled*	9	3
		Uncontrolled	1	4
		D/C, ADR	0	0

D/C=Discontinued.
ADR=Adverse reaction.
*IOP less than 22 mmHg (both eyes).

<22 mmHg in each eye) by the end of the four week period as were 12 (71%) of the timolol treated patients. Five of the nadolol patients who were uncontrolled at this time still had the option of a higher dose regimen. One of these patients proceeded into long-term therapy at a higher dose (40 mg) and achieved control. Another proceeded into long-term at the same dose (40 mg) and also achieved control. There was no statistically significant difference between nadolol treatment and timolol in terms of IOP control at the end of the short-term period.

The distribution of patients by treatment group and dose throughout the short-term period is shown in Table 1. Of the 17 patients on 20 mg of nadolol six progressed to a 40 mg and one to an 80 mg dose. Among 18 patients randomised to 40 mg nadolol one progressed to an 80 mg dose, and among 16 patients starting with an 80 mg dose one was reduced to 40 mg (downward titration was not part of the protocol). Seven of the 17 patients receiving timolol progressed to the more concentrated dosage form. Tables 2 and 3 illustrate the therapeutic outcome of short-term therapy (that is, control or lack of IOP control) according to initial and final dosage. A similar efficacy pattern was observed for the nadolol 20 mg and timolol 0·25% regimens, and for the nadolol 40 mg and 80 mg regimens. However, a majority of the seven patients titrated to the higher concentration of timolol did not show control of IOP.

Mean IOP reductions produced by the dose levels actually employed during weeks 1 and 4 are shown in Table 4. Only those measurements at the end of week 1 provide a comparison of the randomly assigned starting doses, as they were obtained prior to any dose titration. At that time the mean 18·4% IOP reduction achieved with the 20 mg nadolol regimen was less ($p<0{\cdot}05$) than that achieved with the nadolol 40 mg and 80 mg regimens (31·4% and 31% reductions, respectively) but not significantly different from the 0·25% timolol regimen (24·4% reduction).

If nadolol and timolol treatments are considered regardless of dosage, by the end of week four the mean IOP had decreased by 30·7% with nadolol from 27·9 mmHg to 19·1 mmHg, and by 34·6% with timolol from 26·6 mmHg to 17·8 mmHg.

DURATION OF IOP EFFECT

IOP measurements taken immediately prior to the next dose were obtained for all patients towards the end of week 4. Mean pressure reductions 23 to 24 hours after the last nadolol dose and 11 to 12 hours after the last timolol dose are shown in Table 5. Statistical analyses were not made because the original randomisation scheme no longer applied but pressure reductions remained substantial at all dose levels. The IOPs of some patients on the 20 mg and

Table 4 *Mean intraocular pressure (IOP) reductions*

	Actual dose				
	Nadolol 20 mg o.d.	*Nadolol 40 mg o.d.*	*Nadolol 80 mg o.d.*	*Timolol 0·25% b.d.*	*Timolol 0·5% b.d.*
Week 1					
n	17	18	16	17	0
Mean pretreatment IOP	28·6	28·1	27·0	26·7	0
Mean post-treatment IOP	22·6	19·1	18·7	20·3	0
Mean change†	−18·4%*	−31·4%	−31·0%	−24·4%	0
Week 4†					
n	10	23	15	9	4
Mean pretreatment IOP	25·9	28·4	28·4	26·0	28·0
Mean post-treatment IOP	19·5	18·8	19·2	16·1	22·0
Mean change‡	−24·8%	−33·8%	−32·4%	−38·0%	−21·5%

*Differs from mean reductions observed with nadolol 40 mg and nadolol 80 mg, $p<0·05$.
†Statistical analysis inappropriate—original randomisation no longer obtains.
‡Adjusted for pretreatment differences.

Table 5 *Mean intraocular pressure reductions: 23-24 hours after last nadolol and 11-12 hours after last timolol dose**

	Actual dose				
	Nadolol 20 mg o.d.	*Nadolol 40 mg o.d.*	*Nadolol 80 mg o.d.*	*Timolol 0·25% b.d.*	*Timolol 0·5% b.d.*
n	10	23	15	9	4
Mean pretreatment IOP	25·9	28·4	28·4	26·0	28·0
Mean post-treatment IOP	21·6	21·3	21·8	18·0	22·1
Mean change†	−16·6%	−25·0%	−23·4%	−30·8%	−21·1%

*Statistical analysis inappropriate—original randomisation no longer obtains.
†Adjusted for pretreatment differences.

40 mg nadolol regimens in one of our centres (J.D.H.Y.). 'escaped' from control at the 24-hour time point. However, in these patients it was found that the same total daily dose given b.d. was satisfactory.

BLOOD PRESSURE AND HEART RATE

Reductions in blood pressure and heart rate in patients receiving nadolol closely corresponded to those observed in the normal volunteer study.[1] Systolic pressure, diastolic pressure, and heart rate decreases ranged from 5 to 9%, 8 to 10% and 16 to 19%.

IOP CONTROL—LONG-TERM

The clinical course of the 38 patients (33 nadolol and 5 timolol) studied for up to two years is shown in Fig. 2. At the last visit during this period (mean 12·3 months) 25 (76%) of the 33 patients on nadolol were controlled; two were discontinued as treatment failures on 40 mg daily without employing the option of a higher dose; and one was a treatment failure at the maximum dose. Of the five patients entering long-term therapy on timolol two were controlled at the final visit (mean 11·2 months), and the others were discontinued as treatment failures at the maximum 0·5% concentration. Table 6 illustrates the outcome (that is, control or lack of control) for patients on long-term nadolol therapy according to initial and final dosages. All but two of 23 nadolol patients entering long-term therapy on the 20 mg and 40 mg dosages were controlled by one or the other of these regimens, excluding four who were controlled but were discontinued because of adverse drug reactions.

All five patients in one centre (J.W.) who were receiving 80 mg of nadolol at month 12 were reduced to a 40 mg dose and remained controlled at month 24.

SAFETY

Nadolol administered orally had no effect on visual acuity, accommodation, refraction, pupil size, or tear production. During the relatively brief period of this study there was no evidence of visual field deterioration in any patient.

The numbers of patients discontinued as a result of adverse reactions and the treatment regimens employed at the time of discontinuation can be seen

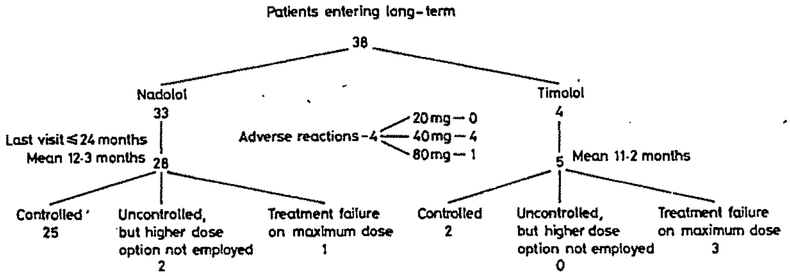
Patients entering long-term
38
Nadolol
33
Last visit ≤ 24 months
Mean 12·3 months
28
Adverse reactions – 4
20 mg — 0
40 mg — 4
80 mg — 1
Timolol
4
5
Mean 11·2 months
Controlled*
25
Uncontrolled, but higher dose option not employed
2
Treatment failure on maximum dose
1
Controlled
2
Uncontrolled, but higher dose option not employed
0
Treatment failure on maximum dose
3

Fig. 2 *The clinical course of patients during long term therapy, up to 24 months.*

Table 6 *Long-term outcome by initial and final nadolol dose*

Dose entering Long-term	*n*		*Final dosage—long-term*		
			Nadolol 20 mg o.d.	*Nadolol 40 mg o.d.*	*Nadolol 80 mg o.d.*
Nadolol 20 mg	5	Controlled*	2	2	0
		Uncontrolled	0	1	0
		D/C, ADR	0	0	0
Nadolol 40 mg	18	Controlled*	1	12	0
		Uncontrolled	0	1	0
		D/C, ADR	0	4	0
Nadolol 80 mg	10	Controlled*	0	5	3
		Uncontrolled	0	0	1
		D/C, ADR	0	0	1

D/C=Discontinued.
ADR=Adverse reaction.
*IOP<22 mmHg (both eyes).

from Fig. 1 and Table 1 (short-term) and from Fig. 2 and Table 6 (long-term).. Overall, eight patients treated with nadolol. (15·7%) were discontinued for such reactions. All but one of them were receiving either 40 mg or 80 mg daily. With the exceptions of one patient with bradycardia and another with palpitations the complaints were 'loss of energy', 'fatigue', and 'tiredness'. Other patients reported mild and transient reactions of a similar nature, but with continuation of therapy symptoms usually abated.

No adverse reactions were reported among the patients treated with timolol.

Discussion

This study of patients with chronic simple glaucoma demonstrates that the IOP lowering effect of orally administered nadolol 20 mg and 40 mg is equivalent to that of a twice daily regimen of 0·25% or 0·5% timolol eye drops. Higher doses of this β blocker, as are commonly used in the management of systemic hypertension, are unnecessary. Nadolol's efficacy is well maintained over relatively prolonged periods of time.

Blood pressure and heart rate reductions for the three doses of nadolol used (20, 40, and 80 mg daily) corresponded closely to those obtained in the normal volunteer study.[1] In that study it was evident that, at the low doses of nadolol used, the ocular effect was considerably greater than the cardiovascular effects. This was not so obvious in our clinic patients, because baseline IOPs were not allowed to reach a maximum untreated level.

In most patients oral nadolol was well tolerated, and some expressed the wish to continue taking tablets rather than return to topical medication. A few patients did incur some of those side effects associated with β blockers, but at the 20 mg daily dosage level only one was discontinued for this reason ('slight tiredness').

Patient preference apart, we conclude that a 20 mg or 40 mg nadolol tablet taken once daily is sufficient to control the IOP of most patients with chronic simple glaucoma. This approach to therapy, we believe, would be preferable to topical medication in two situations; first, for reasons of practicality and cost in patients already receiving β blockers for cardiovascular indications and second, in patients for whom the instillation of eye drops is difficult or (without help) impossible.

References

1 Williamson J, Atta HR, Kennedy PA, Muir JG. Effect of orally administered nadolol on the intraocular pressure in normal volunteers. *Br J Ophthalmol* 1985; **69:** 38–40.

2 Wettrell K, Pandolfi M. Effect of oral administration of various beta-blocking agents on the intraocular pressure in healthy volunteers. *Exp Eye Res* 1975; **21:** 451–6.

3 Ohrstrom A, Pandolfi M. Regulation of intraocular pressure and pupil size by β-blockers and epinephrine. *Arch Ophthalmol* 1980; **98:** 2182–4.

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Role of sodium hyaluronate (Healonid) in triangular flap trabeculectomy

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SUMMARY The role of sodium hyaluronate (Healonid) in trabeculectomy to prevent a shallow or flat anterior chamber and hypotonia in the immediate postoperative period is reported. Twenty-nine eyes of 27 patients were included in a randomised controlled study. Thirteen eyes had trabeculectomy alone, and 16 eyes had trabeculectomy performed with Healonid injected into the anterior chamber. The results showed that shallowing of the anterior chamber and hypotonia occurred in both groups until day 21 postoperatively. There was no statistically significant difference between the two groups ($p>0\cdot05$). Healonid has no significant value in maintaining anterior chamber depth and preventing hypotonia in the early postoperative period following trabeculectomy.

Since trabeculectomy was introduced by Cairns in 1968[1] and later modified by Watson,[2] it has become the most popular filtration procedure in the surgical management of glaucoma. One of the merits is a lower incidence of flat or shallow anterior chambers postoperatively as compared with other filtration surgery.[3-10] The incidence of flat anterior chamber is from 2% to 4·5%, while that of shallowing of the anterior chamber is 5% to 12%.[3-10] The incidence of flat anterior chamber following iridencleisis is as high as 24% and even higher at 37% following Scheie's procedure.[11] Despite the low incidence of flat anterior chambers following trabeculectomy it plays an important part in the development of cataract. 60% of cataracts that developed in the first six months following trabeculectomy had shallow or flat anterior chambers.[10]

Healonid is a high viscoelastic material with the properties of being non-antigenic and non-inflammatory.[12] It is capable of passing through a fine Rycroft cannula, so that it can easily be injected into the eye. It has been used in anterior segment surgical procedures, particularly in lens implantation[13-14] and keratoplasty, as it can maintain a deep anterior chamber which allows surgical manipulation and minimises endothelial cell damage.[15]

There is an uncontrolled study which suggests that Healonid injected into the anterior chamber following trabeculectomy has a beneficial effect in reducing the risk of flat anterior chamber.[12] A randomised controlled study is reported here on the value of Healonid in trabeculectomy for preventing shallow or flat anterior chamber and hypotonia in the immediate postoperative period.

Materials and methods

Patients with open-angle glaucoma, or acute or intermittent closed-angle glaucoma with raised intraocular pressure above 21 mmHg despite maximum medical treatment, were included in the study. Patients for combined cataract extraction and trabeculectomy, aphakic and rubeotic glaucoma, were excluded.

Having been selected for the study the patients were randomly assigned, so that they either had trabeculectomy alone or had trabeculectomy with Healonid injected into the anterior chamber.

Table 1 *Characteristics of patients*

	No Healonid	*Healonid*
Number of eyes	13	16
Mean age	67·5 (52–86)	67·1 (33–80)
Sex: male	5	10
female	8	6
Mean preop. IOP	30·4	28·6
Mean preop. ACD	2·4	2·4
Mean outflow facility	0·06	0·06

IOP=Intraocular pressure. ACD=Anterior chamber depth.

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All patients received full ophthalmological examinations preoperatively. Snellen's visual acuity was recorded, intraocular pressure was measured with a Goldmann applanation tonometer, the depth of the anterior chamber was measured with a Jaeger depth micrometer, gonioscopy was done, outflow facility was recorded by tonography, and the density of cataract, if present, was recorded diagrammatically.

Trabeculectomies were performed under general or local anaesthesia. The surgical technique used is based on that described by Watson[2] with a modification involving the use of a limbal based triangular half thickness lamellar scleral flap measuring 5×5×5 mm.[16] A rectangular 4×2 mm sclerotrabecular lamella is then excised, peripheral iridectomy performed, and the apex of the triangular scleral flap stitched back to the original place with a single 8·0 virgin silk. A corneal paracentesis at 10 or 2 o'clock is made with a Graefe knife at the beginning of the operation so that Healonid can be injected into the anterior chamber through this at the end of the operation, resulting in deepening of the anterior chamber until Healonid is extruded through the trabeculectomy fistula into the subconjunctival space.

All patients were treated with Predsol N eye drops (prednisolone sodium phosphate 0·5%, neomycin sulphate 0·5%, thiomersal 0·005%) four times a day and atropine 1% eye drops twice daily for three weeks postoperatively. They were examined on days 1, 2, 3, 7, 21, and 42 postoperatively, and a record of the intraocular pressure, anterior chamber depth, severity of anterior uveitis, hyphaema, choroidal detachment, and cataract was made.

Results

Twenty-nine eyes of 27 patients were included in the study. Thirteen eyes had trabeculectomy alone of which 12 had open-angle glaucoma, and one acute closed-angle glaucoma. Sixteen eyes had trabeculectomy with Healonid injected into the anterior chamber of which 11 eyes had open-angle glaucoma, two acute closed-angle glaucoma, and three intermittent closed-angle glaucoma. The two groups were comparable for age, sex, preoperative mean anterior chamber depth, intraocular pressure, and outflow

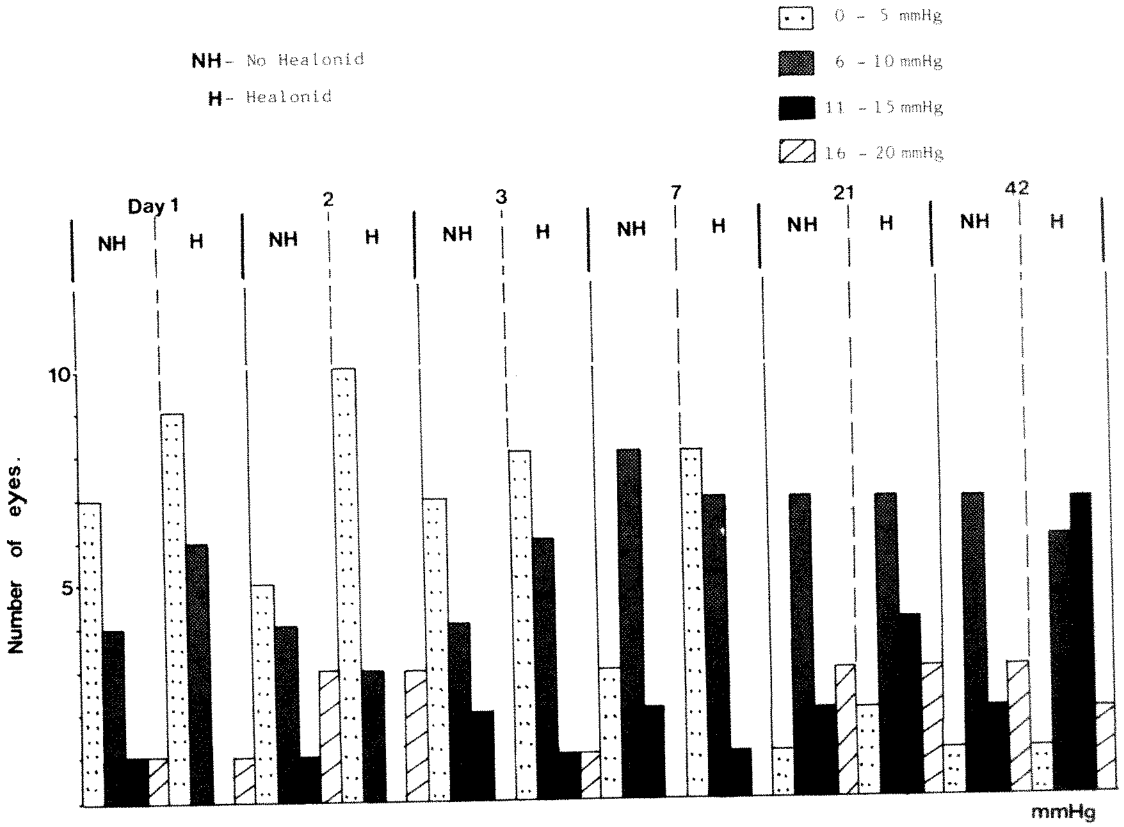

Fig. 1 *Frequency distribution of the amount of shallowing of the anterior chamber.*

Table 2 *Mean anterior chamber depth (mm)*

	Preop.	*Day 1*	*Day 2*	*Day 3*	*Day 7*	*Day 21*	*Day 42*
No Healonid	2·4	1·7	1·9	1·9	1·9	2·4	2·4
Healonid	2·4	1·5	1·3	1·3	1·5	2·3	2·3

facility (Table 1). Two eyes in the Healonid treated group had flat anterior chamber, and there was no flat anterior chambers in the group without Healonid. The frequency distribution of the amount of shallowing of the anterior chamber is shown in Fig. 1. The mean anterior chamber depths are shown in Table 2. There is no statistically significant difference in the two groups as analysed by Student's *t* test (p>0·05).

The frequency distribution of postoperative intraocular pressure is shown in Fig. 2. The mean intraocular pressures are shown in Table 3. There is no statistically significant difference between the two groups as analysed by Student's *t* test (p>0·05). The incidence of hyphaema and choroidal detachment is shown in Table 4. All hyphaemas resolved spontaneously by day seven, and choroidal detachment settled spontaneously by day 21.

Discussion

Two eyes in the Healonid treated group had flat anterior chambers. This occurred in one eye on day seven and was associated with a choroidal detachment. The anterior chamber reformed spontaneously the following day. In the second eye the flat anterior chamber occurred on day four and had to be reformed on day seven. These two eyes subsequently developed anterior subcapsular cataracts.

It is evident from the frequency distribution of the amount of shallowing of the anterior chamber in Fig.

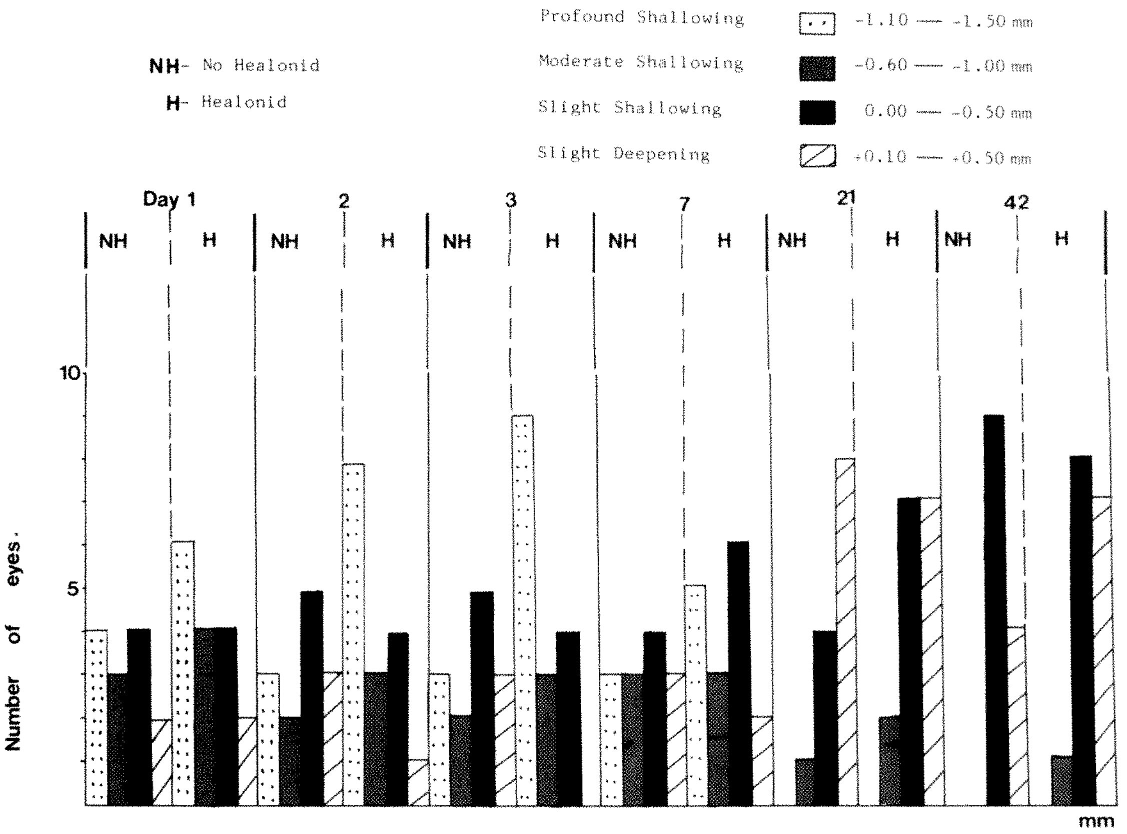

Fig. 2 *Frequency distribution of postoperative intraocular pressure.*

Table 3 *Mean intraocular pressure (mmHg)*

	Preop.	*Day 1*	*Day 2*	*Day 3*	*Day 7*	*Day 21*	*Day 42*
No Healonid	30·4	5·6	7·8	5·7	8·0	10·5	10·6
Healonid	28·6	5·8	7·3	6·1	5·6	10·3	12·8

Table 4 *Other complications*

	No Healonid	*Healonid*
Hyphaema	9 (69·2%)	10 (62·5%)
Choroidal detachment	3 (23%)	7 (44%)

1 that more than 50% of the eyes in both groups had either profound or moderate shallowing of the anterior chamber until day 7. 92% of the eyes in the no Healonid group and 87% of the Healonid treated group had either slight shallowing or slight deepening of the anterior chamber on day 21. The mean anterior chamber depth also returned to preoperative level in both groups on day 21.

From the frequency distribution of postoperative intraocular pressure in Fig. 2 it is clear that there was a higher incidence of hypotonia below 10 mmHg in both groups up to day seven. The mean intraocular pressure above 10 mmHg was attained on day 21 in both groups.

The incidence of choroidal detachment in both groups was higher than in other studies,[3 10] because fundal examination was carried out in search of this complication every time the patient was seen. The eyes with choroidal detachment are associated with profound or moderate shallowing of the anterior chamber. All choroidal detachment resolved spontaneously by day 21 at the same time as the mean anterior chamber depth returned to preoperative level. The results indicate that sodium hyaluronate (Healonid) has no significant value in maintaining anterior chamber depth and preventing hypotonia in the immediate postoperative period.

The use of Healonid for lens implantation is safe and free from complication except for an ocular hypertensive effect.[17] This is because of the presence of a watertight wound following lens implantation. However, in trabeculectomy Healonid will be extruded through the trabeculectomy fistula if there is any rise in intraocular pressure. Indeed, Healonid is seen to accumulate in the subconjunctival space in the lower fornix (Fig. 3) on the first postoperative day in cases where there is profound shallowing of the anterior chamber.

The presence of Healonid in the anterior chamber gives the appearance of plastic anterior uveitis which disappears by the third postoperative day. Although it is not known exactly how long Healonid stays in the anterior chamber, this clinical observation indicates that Healonid leaves the anterior chamber by the third postoperative day after being diluted with aqueous as Healonid is a hydrophilic substance.[12] Therefore, the extrusion of the Healonid through trabeculectomy fistula and the dilution of Healonid with aqueous may be the contributory factors for the failure of Healonid to act as an internal tamponade in the anterior chamber despite its initial high viscoelasticity.

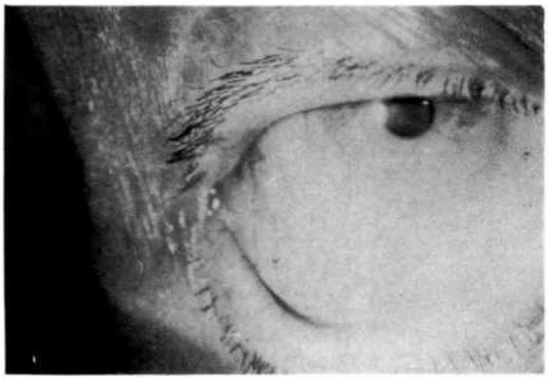

Fig. 3 *Healonid accumulated in the lower fornix.*

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References

1 Cairns JE. Trabeculectomy. *Am J Ophthalmol* 1968; **66:** 673–9.
2 Watson PG. Trabeculectomy, a modified ab externo technique. *Ann Ophthalmol* 1970; **2:** 199–205.
3 Ridgway AEA, Rubinstein K, Smith VH. Trabeculectomy—a study of 86 cases. *Br J Ophthalmol* 1972; **56:** 511–6.
4 Thyer HW, Wilson P. Trabeculectomy. *Br J Ophthalmol* 1972; **65:** 37–40.
5 Watson PG, Barnett F. Effectiveness of trabeculectomy in glaucoma. *Am J Ophthalmol* 1975; **79:** 831–45.
6 McPherson SD Jr, Cline JW, McCurdy D. Recent advances in glaucoma surgery. Trabeculotomy and trabeculectomy. *Ann Ophthalmol* 1977; **9:** 91–6.
7 D'Ermo F, Bonomi L, Duro D. A critical analysis of the long-term results of trabeculectomy. *Am J Ophthalmol* 1979; **88:** 829–35.

8 Murray SB, Jay JL. Trabeculectomy, its role in the management of glaucoma. *Trans Ophthalmol Soc UK* 1979; **99:** 492–4.
9 Zaidi AA. Trabeculectomy, a review and 4-year follow up. *Br J Ophthalmol* 1980; **64:** 436–9.
10 Mills KB. Trabeculectomy: a retrospective long-term follow up of 444 cases. *Br J Ophthalmol* 1981; **65:** 790–5.
11 Scheie HG. Filtration operations for glaucoma: a comparative study. *Am J Ophthalmol* 1962; **53:** 571–90.
12 Balazs EA, Freeman MI, Klöti R, *et al.* Hyaluronic acid and replacement of vitreous and aqueous humour. *Mod Probl Ophthalmol* 1972; **10:** 3–21.
13 Miller D, Stegmann R. Use of sodium hyaluronate in human I.O.L. implantation. *Ann Ophthalmol* 1981; **13:** 811–5.
14 Choyce DP. Healon in anterior chamber lens implantation. *Am Intraocular Implant Soc J* 1981; **7:** 138–9.
15 Pape LG, Balazs EA. The use of Na-hyaluronate in human anterior segment surgery. *Ophthalmology* 1980; **87:** 699–705.
16 Singh D, Singh M. Pretrabecular filtration for secondary glaucoma. *Trans Ophthalmol Soc UK* 1978; **98:** 89–92.
17 Percival SPB. Complications from use of sodium hyaluronate (Healonid) in anterior segment surgery. *Br J Ophthalmol* 1982; **66:** 714–6.

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Effect of age on contrast sensitivity function: uniocular and binocular findings

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SUMMARY Monocular and binocular contrast sensitivity function for a range of spatial frequencies was measured in two groups of subjects with normal vision. Statistically significant differences in performance between the younger group (age 20–30 years) and the older group (age 50–87 years) were found at all spatial frequencies sampled between 0·40 and 19·25 cpd. In the age range 50–87 years there was a linear decline in contrast sensitivity with age for medium and high spatial frequencies, but sensitivity for low spatial frequencies was independent of age.

In recent years a number of investigators have used contrast sensitivity function (CSF) as a supplementary measure of visual performance both in normal subjects[1 2] and in patients.[3–5] Contrast thresholds are measured for a number of different spatial frequencies (the number of repetitions of a grating pattern, usually sinusoidal, within a unit of distance), and the results are represented graphically by plotting the reciprocal of the contrast threshold (contrast sensitivity) as a function of spatial frequency. In this way the performance of the eye can be specified over a wide working range and gives a broader description of visual function than the more conventional tests of visual acuity. Measurement of contrast sensitivity has revealed visual loss in patients with cerebral lesions,[6] multiple sclerosis,[3 7] macular disease,[8] glaucoma,[4 5 9] cataract,[10] and amblyopia.[11]

A number of the above disorders are prevalent among older patients in whom age related changes in the eye are likely to influence the results of visual function tests. It is thought that age related changes, such as those found with visual acuity measurement, are attributable not only to lenticular yellowing and senile miosis but also to neuronal and receptor loss in the visual pathway.[12] The implication that the decline with age in human visual performance is the result of loss of neuronal quality and quantity receives support from other sources. Age related changes in the morphology of human cones[13] and a decrease in the neuron population density of the macular projection areas in the visual cortex[14] have been reported. In a tachistoscopic study Walsh[15] has shown very clearly that there is a decrease in the efficiency of central processing of visual images with age.

Recently age dependent losses of contrast sensitivity have been reported by investigators who have used gratings displayed on an oscilloscope[9 16–20] and the Arden printed test.[9 21 22] Unfortunately the results of these studies do not all agree. Some investigators report a loss of contrast sensitivity for all spatial frequencies,[9 19 21] while others found losses for high and medium spatial frequencies only.[16 17 20 22] One group found losses only at low and medium spatial frequencies.[18] It is likely that this lack of agreement between studies is attributable to a number of procedural differences, to the type of equipment used, and to the small sample sizes in the majority or studies.

Four of the studies investigated visual performance in patients of more than 70 years.[9 18–20] Undoubtedly the study of older normal subjects poses a number of difficulties for the investigator and a definition of 'normal' becomes more difficult with increasing age. However, the incidence rates for disorders such as cataract, glaucoma, and macular disease in which abnormal CSF has been reported increase after the age of 65 years,[23] so that this is an age group for which it is particularly important to obtain normative data in order to be able to evaluate visual dysfunction in relation to age. We have measured CSF in 70 subjects with normal eyes to obtain age norms for clinical use and to form a database for studies of various eye

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disorders. Fifty three of these subjects were aged 50 or more. The remaining 17 subjects were young adults who were included for comparison with the older group.

Materials and methods

Subjects. Seventy Caucasians aged between 20 and 87 years volunteered to take part in the study. None of the subjects had any previous experience in contrast sensitivity measurement techniques. The responses for two different age groups were examined. In the younger age group there were 17 subjects: 7 males, mean age 23 years (range 22–26 years), and 10 females, mean age 25 years (range 20–30 years). In the older group there were 53 subjects: 24 males, mean age 71 years (range 54–81 years), and 29 females, mean age 73 years (range 50–87 years).

Subjects were included in the study if: (a) There was no current eye disorder on clinical examination. (b) There was no previous history of eye disorder that might affect visual function, for example, amblyopia. (c) There was no family history of glaucoma or diabetes. (d) There was visual acuity of 6/9 (decimal 0·66) or better in each eye separately. (e) Optical correction was between −6 dioptres and +6 dioptres inclusive.

Cataract was excluded on the basis of the presence of a black lens opacity silhouetted against the red reflex on ophthalmoscopic examination. Any eye in which such an opacity was observed was excluded from the study. Severity of nuclear sclerosis was assessed in the slit beam on a scale of one to three. A score of one indicated the least sclerosis, and a score of three indicated the most sclerosis. Subjects with a score of two or less in each eye separately were included in the sample.

Glaucoma was excluded on the basis of a careful family history, examination of the optic disc, and applanation tonometry for those aged 70 or more. Subjects with intraocular pressure of less than 21 mmHg were considered to be non-glaucomatous. Senile macular degeneration was excluded on the basis of a morphological absence of macular degenerative change. All but seven of the subjects had visual acuity of 6/6 (1·00) or better in each eye. These seven were subjects in the older age group: five had visual acuity of 6/9 (0·66) in one eye and 6/6 (1·00) or better in the fellow eye, and two subjects aged 81 and 87 had visual acuity of 6/12 (0·50) in one and 6/9 (0·66) in the other. The two eyes with visual acuity of 6/12 (0·50) were excluded from the study. The apparent pupil size for all eyes was greater than 2·5 mm.

Apparatus. Distance visual acuity was measured at 6 m by means of an internally illuminated Snellen chart that conformed to the British standard 4274.[24] The luminance of the chart was 125 cd/m^2. A forced choice method was used to obtain visual acuity measurements.

Stationary vertical sine wave gratings of variable spatial frequency were generated on a display oscilloscope by a two channel computer addressed microprocessor waveform generator.[25] The contrast of the grating pattern was adjusted by a computer linked attenuator. Contrast is defined as $((L_{max}-L_{min})/(L_{max}+L_{min}))$ where L_{max} and L_{min} are the maximum and minimum luminances respectively of the grating bars. A device wired in parallel with the microprocessor permitted the contrast of sinewave gratings to be faded on to the oscilloscope screen over a period of 0·5s before the preprogrammed contrast level was achieved. This device overcomes the problem of stimulating transient mechanisms in the visual system at stimulus onset.[26]

The stimulus area on the oscilloscope screen was rectangular, 30 cm×20 cm, with a matt grey surround extending out to form an area 35 cm×42 cm. The mean screen luminance was 300 cd/m^2 and was independent of the contrast of the spatial frequency being displayed. The frame rate was 100 Hz. Contrast values were linear for the six spatial frequencies which were used (0·4, 0·95, 2·88, 6·73, 12·70, 19·23 cycles per degree of visual angle (cpd)). Changes in contrast of the sinewave gratings and the spatial frequency were either made interactively with the computer or preprogrammed. The subject viewed the screen from a distance of 280 cm and rested his chin on an adjustable rest. The test was described, and the subject was asked to respond to the presence of a vertical grating pattern, however faint, by pressing a hand held buzzer.

A preliminary routine was employed with the use of the interactive mode to establish the approximate range of threshold values for the six spatial frequencies. The gratings were presented on the screen in a pseudo random order at various contrast levels. This sequence provided an opportunity for the subject to become familiar with the grating patterns. An estimation of the contrast range in which the subject's threshold was likely to fall for each spatial frequency was obtained from these measurements and recorded. For each spatial frequency two levels of contrast were used to begin a double staircase sequence. One contrast value was above the predicted contrast threshold, and one contrast value was below.

After the preliminary trial had been completed two preprogrammed sequences were used: a double staircase technique,[27] and the 'up-down transformed response rule' (UDTR) technique.[28] The contrast level at which each double staircase was begun was

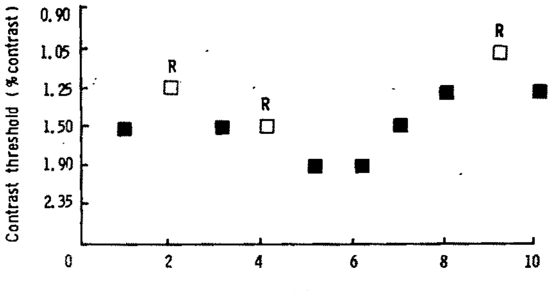

Fig. 1 *A series of responses for the UDTR rule. The change in contrast level is represented on the vertical axis. The trial number is shown on the horizontal axis, and three reversals* R *are shown. The average of the values of the contrast at three reversals gives the value of contrast threshold.* ■*=positive response.* □*=negative response.*

determined by the response recorded in the preliminary trial. The choice of staircase represented on a given trial was made randomly by the computer. For the double staircase the contrast was increased after a negative response and decreased after a positive response. The contrast increment or decrement step was calculated for each presentation as a fraction (0·079) of the previous contrast values.

When the crossover point on the double staircase had been reached a single sequence of stimuli for each spatial frequency value was then presented to the subject (the UDTR rule). The sequence began at the level of the last recorded values for each of the two staircases corresponding to a given spatial frequency. As with the double staircase the contrast was varied in steps of a predetermined size (0·039), but no change in contrast level was made until one of the following patterns of results was obtained at any level:

Decrease contrast after:	Increase contrast after:
YYY or OYY	YYO, OYO, OOO, or YOO
Y=positive response	O=negative response

This set of responses converges on the stimulus level that gives approximately 70% of positive responses (Fig. 1). The threshold was computed from the mean of three reversals.

CSF measurements were made for the right, left, and both eyes of each subject. For the monocular viewing condition the non-viewing eye was covered with an eye patch. In order to assess the reliability of measurements 20 of the subjects (10 males and 10 females) were retested approximately 24 hours after the initial test session.

Results

Monocular and binocular CSF results for the two groups were characterised by a smooth curve which peaked between 2 and 5 cpd and was typically attenuated at low and high spatial frequencies (Fig. 2). Monocular sensitivity was consistently lower than binocular sensitivity for all spatial frequencies. No statistically significant sex differences were found, and so data for male and female subjects were analysed together. In order to assess the reliability of responses the correlation coefficients derived from CSF values on a test-retest basis were examined. For each spatial frequency the correlation between the two test sessions exceeded 0·80 ($p<0·001$).

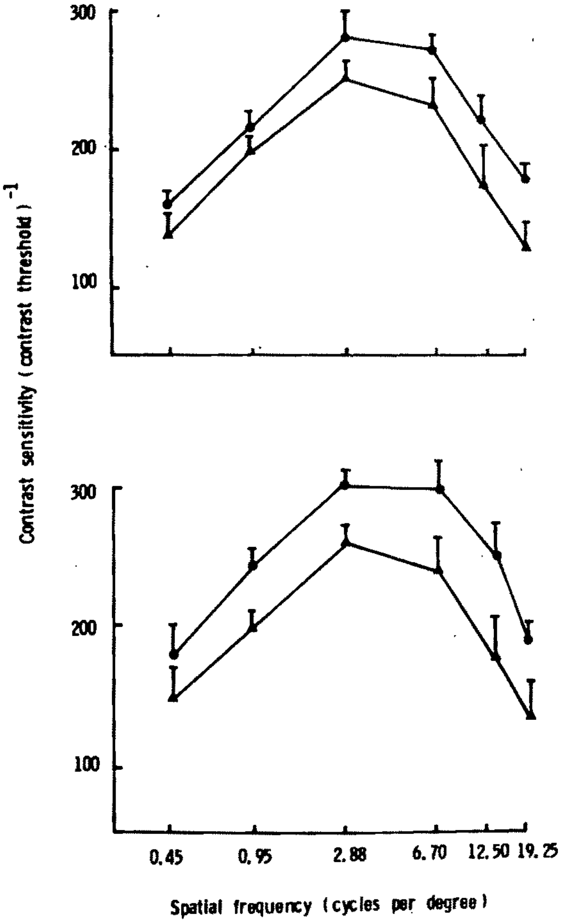

Fig. 2 *Mean contrast sensitivity plotted as a function of spatial frequency for young (●) and old (▲) observers. The top graph shows values for monocular viewing, and the bottom graph for binocular viewing. The vertical bars represent ±1 SD.*

A one way analysis of variance was performed to determine whether the age related contrast sensitivity differences between the younger and older groups of observers were statistically significant (Fig. 2). For both viewing conditions there were significant

Table 1 *Contrast sensitivity function: one way analysis of variance between young and old observers for monocular and binocular viewing*

Spatial frequency (cpd)	*Subjects (age 50–87)*			*Subjects (age 20–30)*				
	Group mean value	*SD*	*Coefficient of variation (SD/mean × 100)*	*Group mean value*	*SD*	*Coefficient of variation (SD/mean × 100)*	*F value*	*Tail p*
Monocular viewing								
0·40	1·435	0·187	13·000	1·648	0·148	8·980	29·89	<0·001
0·95	2·051	0·173	8·386	2·152	0·174	8·080	6·66	0·01
2·88	2·542	0·215	8·457	2·811	0·204	7·250	34·31	<0·001
6·73	2·284	0·312	13·660	2·740	0·196	7·153	54·62	<0·001
12·70	1·736	0·380	21·880	2·219	0·260	11·710	39·88	<0·001
19·25	1·252	0·284	22·680	1·784	0·135	7·560	98·21	<0·001
Binocular viewing								
0·40	1·494	0·212	14·190	1·871	0·212	11·330	61·71	<0·001
0·95	2·098	0·171	8·150	2·376	0·142	5·976	109·43	<0·001
2·88	2·630	0·222	8·440	3·139	0·230	7·327	100·84	<0·001
6·73	2·382	0·291	12·216	3·012	0·235	7·802	106·01	<0·001
12·70	1·836	0·344	18·736	2·522	0·244	9·674	96·65	<0·001
19·25	1·350	0·310	22·960	1·934	0·152	7·859	97·88	<0·001

Table 2 *Regression analysis of monocular contrast sensitivity on age*

CPD	0·40	0·95	2·88	6·73	12·70	19·25
Slope	−0·00307	−0·00285	−0·01203	−0·01472	−0·02017	−0·01578
Intercept 50 year	1·50	2·10	2·80	2·66	2·20	1·61
Pearson product correlation						
r	−0·137	−0·139	−0·486	−0·393	−0·443	−0·464
p	>0·05	>0·05	<0·05	<0·05	<0·05	<0·05

differences among the mean values for the age groups for each spatial frequency (Table 1). Standard deviations for the younger group remained relatively constant over the range of spatial frequencies sampled and were smaller than the standard deviations for the older group. In the older group the standard deviations were greatest for the higher spatial frequencies. The coefficient of variation (the standard deviation of the distribution expressed as a percentage of the mean of the distribution for each spatial frequency) emphasised the greater variability in the frequency distribution in the older subjects.

The responses of the older age group were examined in more detail. A linear regression analysis of contrast sensitivity on age was made for all spatial frequencies. There was a significant decrease in contrast sensitivity with age for all but the two lowest spatial frequencies. The amount of scatter around the regression line was similar for monocular and binocular viewing, the least amount of scatter being found for a spatial frequency of 2·88 cpd in both cases (Table 2).

The older patients were divided into five age groups in order to examine the change with age in visual acuity measurement. However, entry to the study required visual acuity in each eye of 6/9 or better, and so the range of acuities sampled was necessarily limited. The mean visual acuity values for each age group are given in Table 3. There was a statistically significant difference among the means of the five age groups. The main effect for age was significant (F(4,99)=16·40, p<0·01). The relationship between a given level of visual acuity (6/5, (1·2), 6/6 (1·00), 6/7·5 (0·80), or 6/9 (0·66)) and contrast sensitivity function was examined. A one way analysis of variance was performed, and no significant difference was found among the mean CSF values for the four acuity levels. However, for the highest two spatial frequencies there was a rank order fall of contrast sensitivity with each level of visual acuity.

Table 3 *Mean visual acuity values for older subjects*

Age group (years)	*Group mean: log minimum angle of resolution*	*Snellen equivalent*
48–60 n=20 eyes	$\bar{1}$·9	6/5
61–70 n=22 eyes	0·0	6/6
71–75 n=18 eyes	0·0073	6/6
76–80 n=24 eyes	0·04	>6/7·5
81 and over n=20 eyes	0·10	6/7·5

Discussion

We measured contrast sensitivity function in two groups of normal subjects, first, to make a comparison of results between the older and the younger subjects, and second, to examine the pattern of results over a broad age range in 53 older subjects. The study was conducted to obtain age norms for clinical use and to form a database for studies of various eye disorders. In addition to monocular testing binocular assessments were performed in order to relate the results of visual function tests to visual performance as part of a wider study.[29]

The results showed that older observers had reduced contrast sensitivity for all spatial frequencies when compared with their younger counterparts. This was particularly marked for medium and high spatial frequencies. In the age range 50 to 87 years there was a linear decline in CSF with age for medium and high spatial frequencies. Within this age range the responses to low spatial frequencies appeared to be independent of age. These findings are in close agreement with many of the existing data obtained using oscilloscope generated gratings[16 17] and printed tests,[19 22] but are opposed to those of Sekuler and Hutman,[18] who found low but not high spatial frequency changes with increasing age.

Vaegan and Halliday[9] consider that the most important reason for Sekuler and Hutman's[18] contrary findings is that their elderly sample was not representative, because 10 subjects had 6/6 (1·00) vision or better in the tested eye. They argue that the subjects came from a group with particularly high visual acuity for the age range who do not have the same visual performance for lower spatial frequencies. However, the older subjects used in the present study by reason of selection criteria suffer from the same bias, in that the observed Snellen visual acuities are better than one might expect in a representative sample of people in the older age range. Yet no age dependent changes for low spatial frequencies were observed. In a more recent study by the same group using a larger sample[20] the authors found that sensitivity to medium and high spatial frequencies decreased with age after about 40 years. As the same method to determine contrast thresholds was used in both studies, it is possible that the age dependent low frequency attenuation of sensitivity in the first study[18] is attributable to biases introduced by using a small population sample.

Thus there appears to be little evidence for preferential sensitivity losses at low spatial frequencies with aging. It is well known that degradation of any mechanical system, such as radios or hi-fi sets, results primarily in the loss of high frequency information. The visual system reacts in a similar manner to degraded images.[30] It is the low spatial frequency information which conveys the major information about everyday objects as has been demonstrated in studies of face recognition[30 31] and letter recognition.[32] So while it seems likely that aging changes at cellular level occur for neurones mediating both high and low spatial frequency information, these changes are less likely to show themselves in response to low frequency stimuli.

The question whether senile miosis contributes to the reduction of CSF with age has been raised by a number of investigators.[17-19] Derefeldt, Lennerstrand, and Lundh[17] do not give pupil sizes in their publication, but in the studies of Sekuler and Hutman[18] and McGrath and Morrison[19] the pupil sizes were greater than 2 mm as were those in the present study. Senile miosis may not affect contrast sensitivity as such. Other contributory factors may be involved. However, Woodhouse[33] has shown that in the presence of clear optical media, and with screen luminance values above 34 cd/m^2, the difference between spatial frequencies resolved at pupil diameters between 2 and 4 mm is minimal at both high (0·97) and low (0·11) contrasts. In the present study the subjects had clear media, the screen luminance was well above 34 cd/m^2, and the minimum pupil size was greater than 2·5 mm. The limiting effects of diffraction can be dismissed at this pupil size, which suggests that in this study senile miosis is unlikely to be a contributory factor in the reduction of contrast sensitivity with age.

It appears from the present data that, in common with a number of other visual functions, CSF declines with age and in particular at the medium and high spatial frequency end of the curve. The existing data are commensurate with this finding, though lack of standardisation of stimuli and psychophysical procedures from laboratory to laboratory has resulted in variations as to the magnitude and exact location of the sensitivity loss on the contrast sensitivity curve. Responses to stimuli at the low spatial frequency end of the spectrum were independent of age in the subjects over 50 years old in the present study and in the majority of other studies. When pathological status is assessed there are obvious advantages for the use of stimuli which are relatively immune to aging effects in the visual system. An added advantage of the use of low spatial frequencies is that the effects of optical aberration are minimal at this end of the CSF curve.[1]

There is great potential for the application of CSF testing in a number of visual disorders. In the present study a series of age norms is presented for six spatial frequencies with the use of a rigorous testing scheme. Though it is clear that different investigators will present findings based on the particular arrangements available to them, there is a need to standardise approaches in order to make CSF testing more generally useful and available.

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References

1 Campbell FW, Green DG. Optical and retinal factors affecting visual resolution. *J Physiol (Lond)* 1965; **181:** 576–93.
2 Banks MS, Salapatek P. Contrast sensitivity function of the infant visual system. *Vision Res* 1976; **16:** 867–9.
3 Regan D, Silver R, Murray R. Visual acuity and contrast sensitivity in multiple sclerosis—hidden visual loss. *Brain* 1977; **100:** 563–79.
4 Arden GB, Jacobson JJ. A simple grating test for contrast sensitivity: preliminary results indicate value in screening for glaucoma. *Invest Ophthalmol Visual Sci* 1978; **17:** 23–32.
5 Atkin A, Bodis-Wollner I, Wolkstein M, Moss A, Podos S. Abnormalities of central contrast sensitivity in glaucoma *Am J Ophthalmol* 1979; **88:** 205–11.
6 Bodis-Wollner I, Diamond SP. The measurement of spatial contrast sensitivity in cases of blurred vision associated with cerebral lesions. *Brain* 1976; **99:** 695–710.
7 Bodis Wollner I, Hendley CD, Mylin LH. Thornton J. Visual evoked potentials and the visuogram in multiple sclerosis. *Ann Neurol* 1979; **5:** 40–7.
8 Sjostrand J, Frisen L. Contrast sensitivity in macular disease. *Arch Ophthalmol* 1977; **55:** 507–14.
9 Vaegan, Halliday BL. A forced-choice test improves clinical contrast sensitivity testing. *Br J Ophthalmol* 1982; **66:** 477–91.
10 Hess RF, Woo G. Vision through cataracts. *Invest Ophthalmol Visual Sci* 1978; **17:** 428–35.
11 Hess RF. Contrast sensitivity assessment of functional amblyopia in humans. *Trans Ophthalmol Soc UK* 1979; **99:** 391–97.
12 Weale RA. Senile changes in visual acuity. *Trans Ophthalmol Soc UK* 1975; **95:** 36–8.
13 Marshall J. *Ageing changes in human cones.* Proceedings of the 23rd International Congress of Ophthalmology, Kyoto, May 1978. Amsterdam: Excerpta Medica, 1978: **1:** 375–8.
14 Devaney KO, Johnson HA. Neuron loss in the aging visual cortex of man. *J Gerontol* 1980; **35:** 836–41.
15 Walsh DA. Age differences in central perceptual processes. A dichoptic backward masking investigation. *J Gerontol* 1976; **31:** 178–85.
16 Arundale K. An investigation into the variation of human contrast sensitivity with age and ocular pathology. *Br J Ophthalmol* 1978; **62:** 213–5.
17 Derefeldt G, Lennerstrand G, Lundh B. Age variations in normal human contrast sensitivity. *Acta Ophthalmol (Kbh)* 1979; **57:** 679–90.
18 Sekuler R, Hutman LP. Spatial vision and aging I. Contrast sensitivity *J Gerontol* 1980; **35:** 692–9.
19 McGrath C, Morrison JD. The effects of age on spatial frequency perception in human subjects *Q J Exp Physiol* 1981; **66:** 253–61.
20 Owsley C, Sekuler R, Siemsen D. Contrast sensitivity throughout adulthood *Vision Res* 1983; **23:** 689–99.
21 Skalka HW. Effect of age on Arden grating acuity *Br J Ophthalmol* 1980; **64:** 21–3.
22 Sokol S, Domar A, Moskowitz A. Utility of the Arden grating test in glaucoma screening: high false positive rate in normals over 50 years of age. *Invest Ophthalmol Visual Sci* 1980; **19:** 1529–33.
23 Department of Health and Social Security. *Blindness and partial sight in England 1969–1976.* London: HMSO, 1979. Reports on public health and medical subjects No 129.
24 British Standards Institution. *Specifications for test charts for determining distance visual acuity.* British Standard Specification 4274, 1968.
25 Taylor P. A microprocessor controlled gratings generator. *J Physiol (Lond)* 1978; **284:** 20P–1P.
26 Kulikowski JJ, Tolhurst DJ. Psychophysical evidence for sustained and transient detectors in human vision. *J Physiol (Lond)* 1973; **232:** 149–62.
27 Cornsweet T. The staircase method in psychophysics *Am J Psychol* 1962; **75:** 485–91.
28 Wetherill GB. Sequential estimation of quantal response curves. *J R Statist Soc Series B* 1963; **25:** 1–48.
29 Ross JE. The functional effects of visual disorder. DPhil thesis, Oxford University 1983; (Unpublished).
30 Ginsburg AP. Specifying relevant spatial information for image evaluation and display design. An explanation of how we see certain objects. *Proc Soc Information Display* 1980; **21:** 219–27.
31 Owskley C, Sekuler R, Boldt C. Aging and low-contrast vision: face perception. *Invest Ophthalmol Visual Sci* 1981; **21:** 362–5.
32 Ginsburg AP. Relationship between the detection and recognition of Snellen letters and contrast sensitivity for normal and abnormal visual systems. *J Opt Soc Am* 1978; **68:** 1455.
33 Woodhouse JM. The effect of pupil size on grating detection at various contrast levels. *Vision Res* 1975; **15:** 645–8.
34 Green DG, Campbell FW. Effect of focus on the visual response to a sinusoidally modulated spatial stimulus. *J Opt Soc Am* 1965; **55:** 1154–7.

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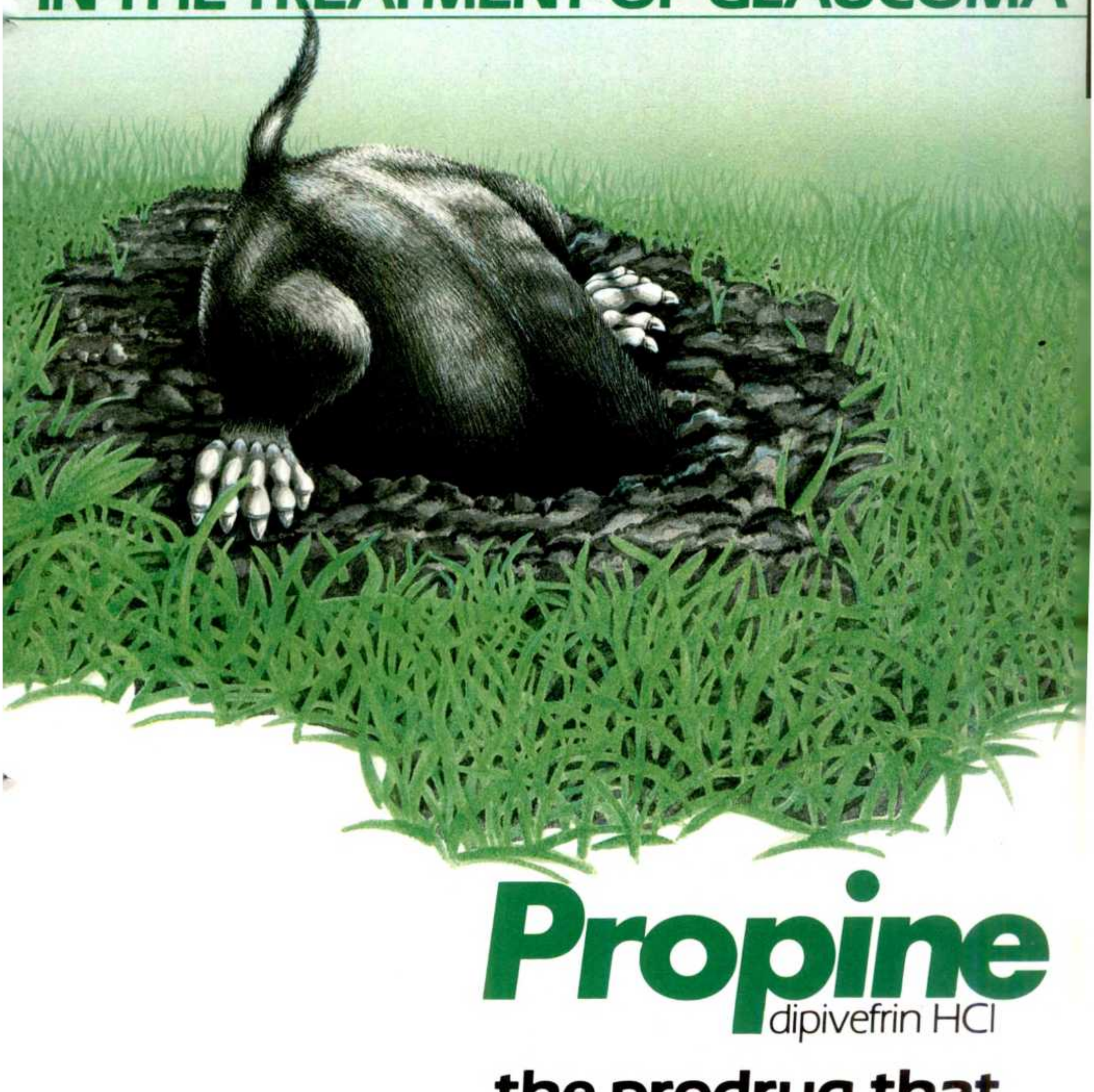

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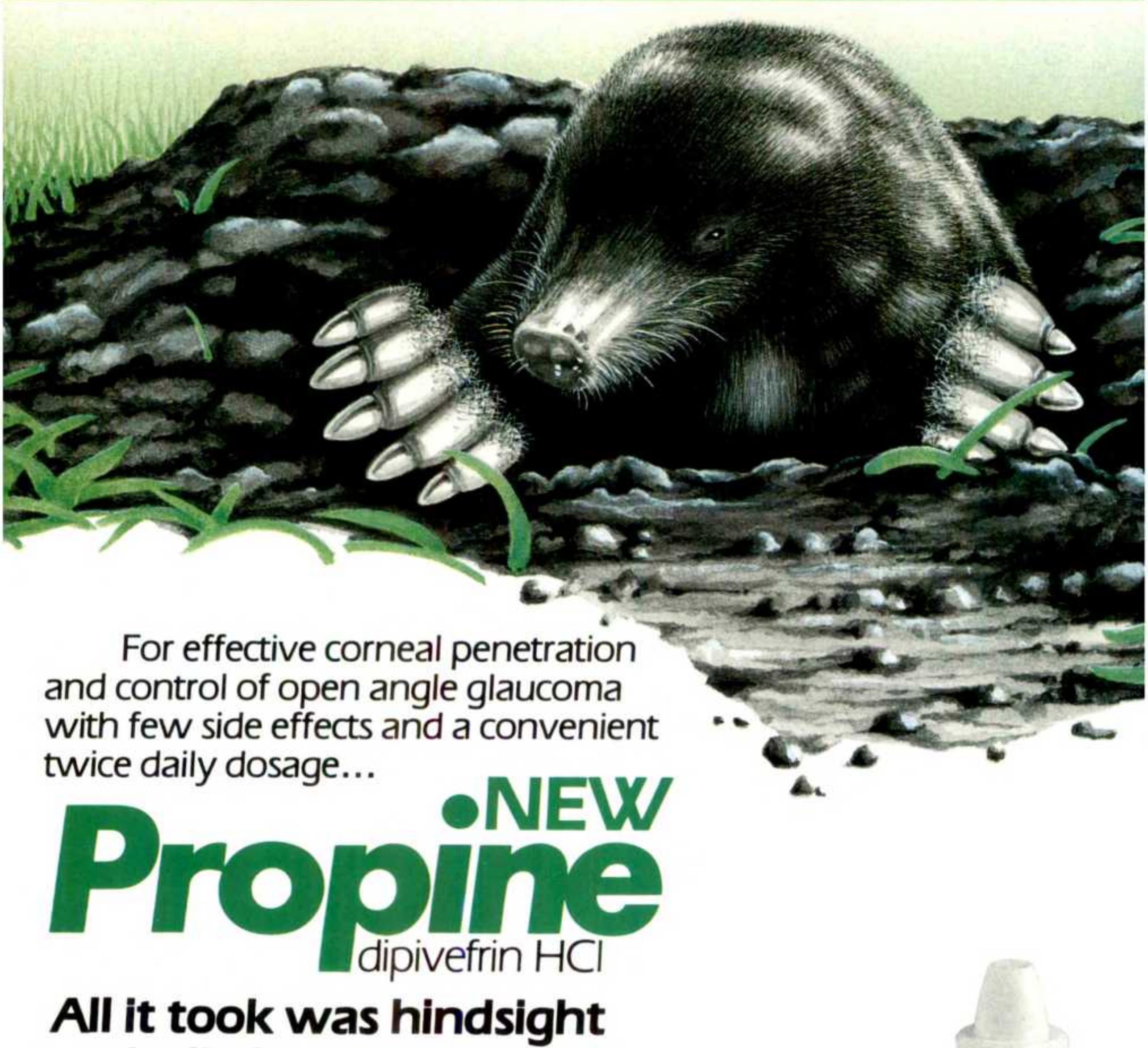

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Congenital fibrosis of superior rectus and superior oblique: a case report

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SUMMARY A rare case of possible postinflammatory fibrosis of the superior rectus and superior oblique muscles, resulting in marked hypotropia with pseudoptosis, is described, together with the surgical management.

Agenesis or hypoplasia of one or more extraocular muscles has been rather infrequently reported. Absence or hypoplasia of the superior rectus[1] and inferior rectus[2] in addition to the horizontal recti has been reported. However, combinations of various muscle anomalies have been less often reported—superior and inferior recti,[3] lateral and inferior recti.[4] Posey[5] reported one case of absence of the inferior rectus treated by the Hummelsheim operation. Silverman and Fletcher[6] reported a case of absence of the inferior oblique and an abnormal insertion of the superior rectus and another case of absent medial rectus and superior oblique with abnormal insertions of other muscles. Starkiewiez[7] reported a case of absence of the trochlea. Prakash *et al.*[8] have reported maldevelopment of the superior oblique and its fascial check mechanism.

Case report

A 7-year-old girl was admitted with a history of downward deviation, ptosis, and defective vision in the right eye since birth. Her birth had been at full term, was normal, and with no history of birth trauma. The mother did not have any illness during pregnancy. All the girl's physical and mental milestones were normal, and she had never had diplopia. She was prescribed glasses a year ago and was referred to us for cosmetic surgery.

General physical examination did not reveal any significant abnormality. Local examination showed slight facial asymmetry, a visual acuity of 1/60 which improved to 3/60 with +6·0 D sph in RE, and 6/60 improving to 6/18 with +4·5 D sph; 0·5 D cyl+90° in LE.

The right orbit appeared to be set at a lower level than the left. There was ptosis in the RE (Fig. 1). Ocular movement in the RE showed marked restriction of elevation in adduction and abduction and slight restriction of depression in abduction and adduction. A thick fibrous band was felt through the skin of the upper lid, extending as a cord in the upper nasal quadrant between the orbital roof and eyeball. Ocular movements were essentially normal in the left eye.

There was marked hypotropia with exodeviation of the RE. Fixation could not be judged owing to congenital moderate degree of horizontal jerky nystagmus.

Measurements of deviation on synoptophore were as given below:

−10° L/R 44		−15° L/R 46
	−10° L/R 20	
−10° L/R 10		−12° L/R 10

No binocular functions could be elicited. Fundus examination revealed a hypermetropic appearance with dull foveal reflex in RE. *X*-ray of the orbit and skull did not show any significant abnormality.

The patient was admitted to hospital for cosmetic squint surgery after a forced duction test under general anaesthesia. The forced duction test showed a marked restriction of elevation in adduction and abduction and a moderate restriction of depression in both adduction and abduction.

On exploration it was seen that superior rectus and superior oblique could not be isolated. Instead a firm, thick fibrous band was adherent to the sclera, extend-

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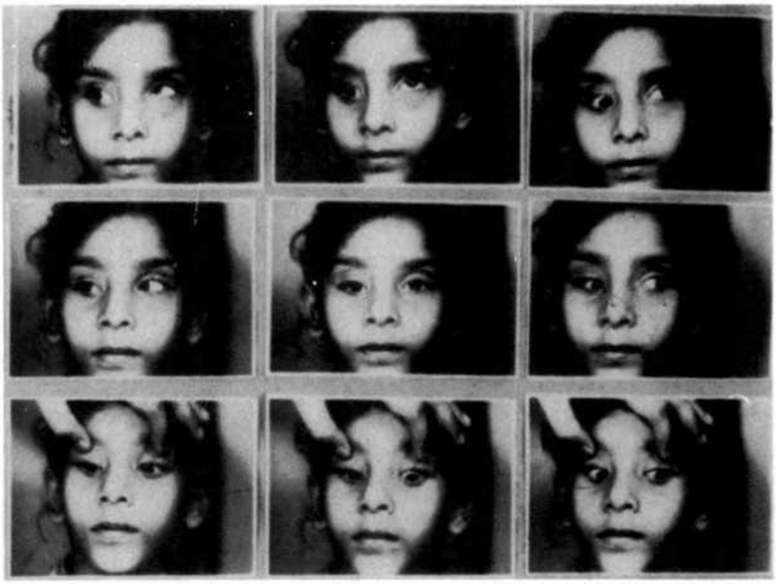

Fig. 1 *Before operation. Right hypotropia in primary position with ptosis in RE. There is a marked restriction of right eye on dextro- and laevo-elevation.*

ing upward and nasally towards the trochlea. The anterior limit of this band was 9 mm on the temporal side and 7 mm on the nasal side from the limbus (Fig. 2). The band was carefully dissected away from the sclera, with resulting free passive movements of the eye ball in all directions. The fibrous tissue was found to be attached to the episcleral tissue and was separated by a careful dissection.

Reassessment after the operation showed almost the same amount of right hypotropia as preoperatively, with the same amount of restriction of 'active movements.' A second operation was therefore undertaken in which Knapp's procedure (transposition of medial and lateral rectus to the superior rectus insertion area) was done in the right eye. The medial rectus in the right eye was found to be inserted only 4 mm away from the limbus. Postoperatively about 10° of right hypotropia persisted, and the cosmetic appearance was unsatisfactory, especially in elevation. So in a third operation the left superior rectus was recessed by 4 mm and the left inferior oblique recessed by 8 mm. This resulted in a very satisfactory cosmetic alignment of the eye. The ptosis in the right eye also had corrected itself (Fig. 3).

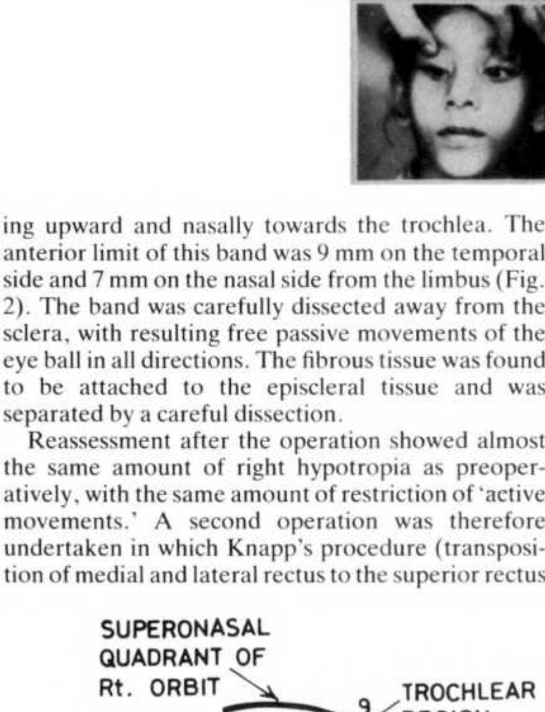

Fig. 2 *The area of adherence of the fibrosed band and its possible course.*

Discussion

With the restricted movements in laevo-elevation with the presence of a fibrous band palpable in the upper nasal quadrant of the orbit the case appeared clinically to be an atypical presentation of superior oblique sheath syndrome. However, the restriction of movement in dextro-elevation and dextro-depression did not support this diagnosis. The possibility of a musculofascial anomaly was entertained.

Reports are lacking of any instance of a combined anomaly of the superior oblique and superior rectus in the same eye or even a total absence of the two. As the two muscles develop from different segments of the mesoderm, it is difficult to explain the genesis of this defect. As discussed by Duke-Elder,[9] there are two main views on the embryological development of the extraocular muscles. According to Lewis[10] the muscles are developed from a single common premuscle mass, appearing at the 7 mm embryonic stage, which extends anteriorly and splits into rudiments supplied by 3 cranial nerves at the 10 mm stage. If this

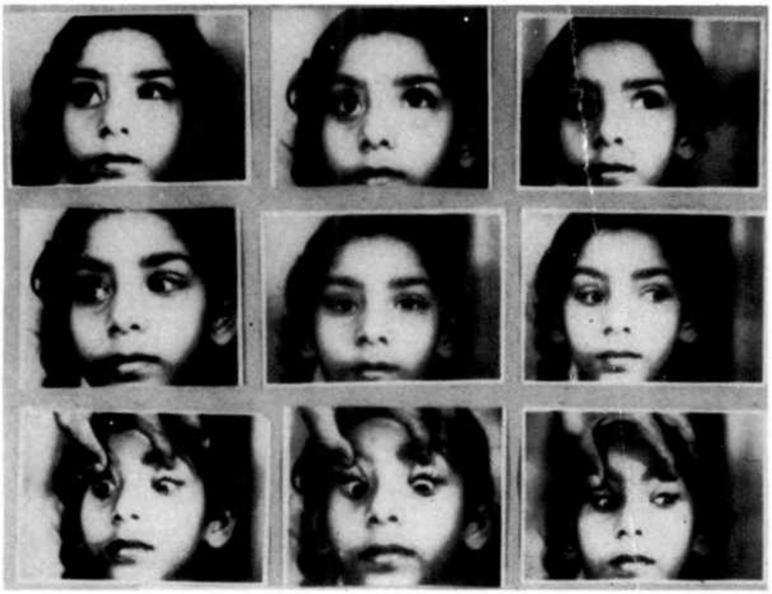

Fig. 3 *After third operation. Improvement of ptosis in RE and marked improvement in the cosmetic appearance on elevation of eye.*

is so, any interference with the superior aspects of the globe might hinder the development of the 2 muscles lying there.

But the more generally accepted view is that of Gilbert,[11] who considers that the extraocular muscles arise from 3 independent but closely related mesodermal condensations supplied by the third nerve from premandibular condensation, and by the fourth and sixth nerves from two separate condensations lying in close contact with the superior rectus anlage. The boundaries of these two muscles become defined only at the 10 mm stage and start separating from each other. Any hindrance to mesodermal development in this region during these stages may also interfere with the development of the superior rectus and superior oblique.

If we envisage a hindrance to the development at such an early stage, it is inevitable that the levator palprebrae superioris would also be affected. Yet on the contrary it was seen after the three operations and the correction of the hypotropia that the levator was perfectly normal, the ptosis having automatically disappeared. So for the lesion to have involved the superior rectus and superior oblique while sparing the levator it must have occurred after the 55 mm stage, when the levator had already separated from the superior rectus. Owing to the close proximity of the superior rectus and superior oblique at this insertion it is possible for an intrauterine inflammation to have involved the two muscles. The clinical finding of a fibrous band across the superonasal quadrant of the orbit shows it to be in the region of the superior oblique tendon, which seems to have become involved in postinflammatory fibrosis along with the superior rectus. The anterior limits of the fibrous tissue almost coincided with the insertion of the superior rectus.

References

1 Steinheim. *Klin Monatsbl Augenheilkd* 1877; **15:** 99. Cited in: Duke-Elder S. *System of ophthalmology*. London: Kimpton, 1973; **6:** 737.

2 Cooper EL, Milk RO, Greenspan JA. Congenital absence of the inferior rectus muscle. *Arch Ophthalmol* 1971; **86:** 451–4.

3 Natale. *Arch Oftalmol B Aires* 1929; **4:** 14.

4 Walker JPS. Congenital absence of inferior and external rectus muscles. *Br J Ophthalmol* 1954; **38:** 631.

5 Posey WC. Anomalies of the eye muscles. *Trans Am Acad Ophthalmol Otolaryngol* 1924; **28:** 243.

6 Silverman SJ, Fletcher MC. Agenesis of three extraocular muscles. A case report. *Am J Ophthalmol* 1965; **60:** 919–22.

7 Starkiewicz. *Klin Oczna* 1967; **37:** 897. Cited in: Duke-Elder S. *System of ophthalmology*. London: Kimpton, 1973; **6:** 737.

8 Prakash P, Diwan C, Khośla PK, Gahlot DK, Tewari HK. Abnormal insertion of superior oblique muscle. *East Arch Ophthalmol* 1974; **2:** 237–40.

9 Duke-Elder S. *System of ophthalmology*. London: Kimpton, 1963; **3**.

10 Lewis WH. In: Keibal F, Hall FB, eds. *Manual of embryology*. Philadelphia and London: 1912: **2**. Cited in: Wolf E. *Anatomy of the eye*. 7th ed. London: Lewis, 1976.

11 Gilbert PW. The origin and development of the head cavities in the human embryo. *J Morphol* 1952; **90:** 194–8.

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Perilimbal vascular anomaly associated with ipsilateral en coup de sabre morphoea

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SUMMARY An unusual case of red eye is described where preceding ipsilateral en coup de sabre morphoea is associated. The suggested aetiology of morphoea and its ocular associations are described.

Case report

A 58-year-old woman was concerned about her bloodshot left eye and the blueness of the upper lid (Fig. 1). The bloodshot eye had worsened during the last two years, but there were no other significant symptoms, and a subjective bruit was denied.

She had suffered from migraine since her youth. She was investigated by a neurologist in 1972 after a severe bout of migraine. Her history suggested a right sided subarachnoid haemorrhage, but this was not confirmed. In 1974 and 1978 stiffness in her joints and back pain were investigated. On examination there was no pulsatile proptosis, no cranial nerve defect, no carotid bruit, and no conjunctival chemosis. Visual acuity was 6/5 in the right eye, and 6/6 in the left eye. Slit lamp examination and fundus examination were normal as was applanation tonometry. However, there was an atrophic area of skin on her forehead (Fig. 2). This had the characteristic appearance of classical morphoea with contraction and firmness of the area, alopecia, and ivory skin with areas of telangiectasis and hyperpigmentation. The position of this morphoea was frontoparietal, and was recognised as sclerodermia en coup de sabre (a sabre blow).

The lesion began as an inflamed area and progressed to become atrophic and fibrotic over the 18 years prior to her eye complaint. This previously normal skin had never had a significant direct trauma or burn, though two years prior to the development of acute phase morphoea there was a car mirror injury to the posterior parietal scalp on the same side.

Investigations made prior to dermatological diagnosis included: conjunctival culture and scrape; full blood count and erythrocyte sedimentation rate; chest x-ray and electrocardiogram; x-rays of skull, orbits, and optic foramina; thyroid function; technetium-99 scan; encephalogram; lumbar puncture; Wassermann reaction; and examination of sacroiliac joints. All were negative. The skull x-ray showed ipsilateral hyperostosis frontalis.

As her only complaint was cosmetic (there were no headaches, neurological, or other ophthalmological conditions), invasive investigations such as biopsy, venography, and carotid angiography were thought not to be justified.

Argon laser treatment to occlude limbal vessels was attempted, but the patient was intolerant. Cautery or cryotherapy to proximal feeding and draining vessels may be tried later. There is no recommended treatment for local morphoea. At follow-up one year later this woman was fit and well with no further eye change. However, she believes that the same signs of tightness and atrophy on her forehead are starting to appear on the upper left cheek. This may be a progression of the en coup de sabre.

Discussion

Morphoea is a localised form of scleroderma and usually has no systemic effect. It regresses and has a benign prognosis. En coup de sabre is a linear groove that usually starts in the frontoparietal region but may extend down to the cheek, nose, lip, or chin. It has many associations, particularly ocular.[1] The cause of morphoea is unknown, but previous trauma is suspected. It has been suggested that this trauma

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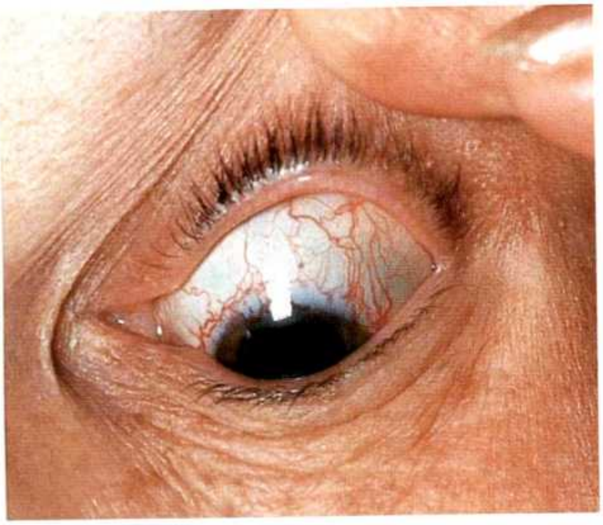

Fig. 1 *Perilimbal vascular anomaly.*

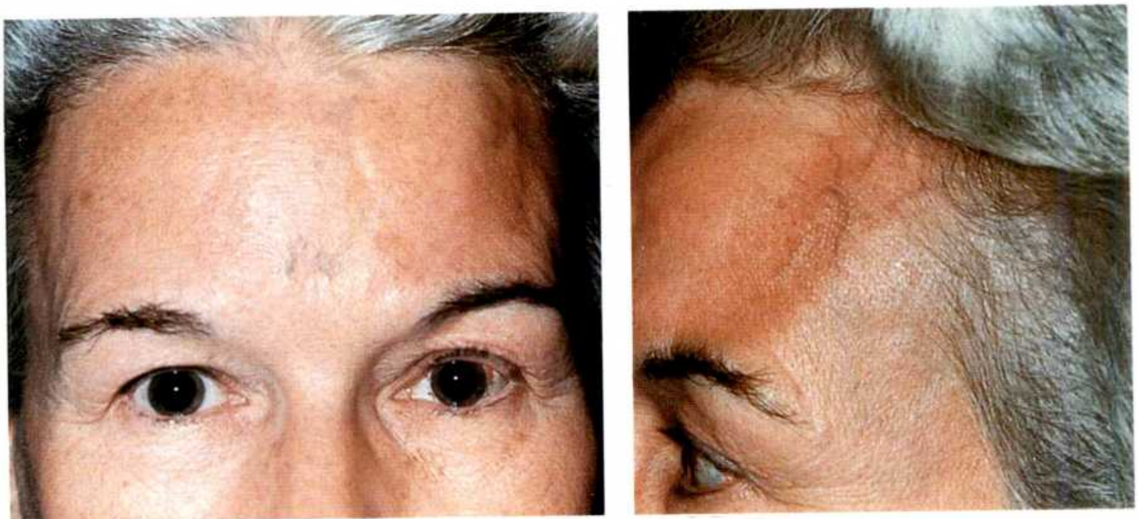

Fig. 2 *Left frontoparietal en coup de sabre morphoea with ipsilateral perilimbal vascular anomaly.*

may induce an autoimmune reaction. Scleroderma is seen in the graft versus host syndrome. Panayai[2] claimed that a cell mediated immune reaction caused chronic tissue damage. The pathology of morphoea (dermis) supports this. In the acute phase there is swelling and a chronic inflammatory reaction. Lymphocytes, plasma cells, and monocytes are prominent, and there is atrophy of the skin appendages. It seems that wherever there is an area of morphoea it is possible that the underlying area may have an associated abnormality such as skin or bone change and, in the case of en coup de sabre, ocular abnormalities. Saad and Khoo[3] described complete cleft lip and palate that developed in association with morphoea of the face in a previously outwardly and radiologically normal child.

The most commonly associated ocular conditions include: skin atrophy and loss of sensation; sector iris atrophy and heterochromia; raised intraocular pressure, and external ocular muscle paresis; and ptosis. Others reported include: lid lash problems and entropion or ectropion (Nancarrow *et al*[4] discussed management of scleroderma of the eyelids causing ectropion with the use of skin grafts); decreased corneal sensation and corneal dystrophy; lens opacity; vitreal haemorrhage; choroiditis; optic nerve atrophy; myositis; skull and EEG changes. Follow-up should be directed towards monitoring and controlling previous abnormalities and notice taken of the possible development of further associations. In conclusion it is believed that the perilimbal vascular anomaly and the preceding morphoea on the same side are directly related.

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References

1 Perrot H, Durand L, Thivolet J, Millon M, Ortonne JP. Sclérodermie en coup de sabre et glaucome chronique homo-lateral. *Ann Dermatol Venereol* 1977; **104:** 381–6.
2 Panayai GS. The immunopathology of connective tissue disorders. *Medicine (Baltimore)* 1979; **14:** 686–9.
3 Saad MN, Khoo CTK. Localized scleroderma of the premaxilla and upper lip. *Br J Plast Surg* 1980; **33:** 245–50.
4 Nancarrow JD, Salah MAJ. A rare case of severe bilateral ectropion from scleroderma. *Plast Reconstr Surg* 1981; **67:** 352–4.

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Retinal pathology in the Kearns-Sayre syndrome

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SUMMARY Examination of the retinal tissues obtained at necropsy from a 14-year-old boy with Kearns-Sayre syndrome showed marked photoreceptor and pigment epithelial cell loss in the retinal periphery and around the optic nerve head. Electron microscopy of surviving retinal pigment epithelial (RPE) cells indicated a loss of apical microvilli and basal infoldings. The RPE was unusually devoid of melanosomes and showed no evidence of phagocytosis of photoreceptor debris. The cytoplasm of the RPE contained numerous, often enlarged, mitochondria. These structural changes suggested that a breakdown in the energy dependent interrelationships between the RPE and the photoreceptor layer was responsible for the outer retinal degeneration. The finding of numerous macrophages in the subretinal space suggests a secondary inflammatory component in the retinal degeneration.

This paper presents the histopathological and ultrastructural findings in the well preserved retinal tissues of a 14-year-old boy suffering from Kearns disease of infantile onset or Kearns-Sayre syndrome. Two years prior to death the boy was night blind and had an obvious pigmentary retinopathy. The basic abnormality in this rare systemic disorder is thought to be a disturbance in mitochondrial morphology and function that is assumed to cause a breakdown in photoreceptor maintenance and phagocytosis. Previous morphological records of the disease in the retina are confined to six studies with the use of light microscopy[1-6] and two investigations by electron microscopy.[7-8] The discrepancies present in the previous morphological descriptions suggest that the syndrome is more complex than first thought. A detailed morphological study was therefore justified, and our findings are discussed in relation to the previously reported material.

Case report

A boy, the fourth child of healthy, non-consanguineous Scottish parents, was born at term after an uneventful pregnancy, birth weight 3 kg, length 52 cm, head circumference 35 cm. There were no neonatal problems, but during the first year failure to thrive and psychomotor delay were noted.

At 13 months the child was admitted to hospital with pallor and gingival bleeding. Peripheral blood examination showed pancytopenia (Hb 5·34 g/dl, leucocytes $3{\cdot}4\times10^9$/l, 5% polymorphs, platelet count 23×10^9/l). Bone marrow aspirate showed marked hypoplasia of all cell lines. The patient was transfused with red cell concentrate and made a good recovery. The hypoplasia was regarded as transitory, and no further haematological abnormality was noted at follow-up.

He walked at 3 years, spoke sentences at 5, and attended a special school. At 7 years the following features were noted: short stature, mental retardation (IQ 64), cerebellar ataxia, dysarthria, bilateral ptosis (Fig. 1), progressive external ophthalmoplegia, decreased visual acuity, atrophic maculae, punctate cataracts, sensorineural deafness, generalised muscle weakness, diminished tendon reflexes, and hyperventilation.

Investigations showed partial growth hormone deficiency, metabolic acidosis, raised serum pyruvate and lactate, and restrictive lung disease. Chromosome karyotype was normal. A muscle biopsy (quadriceps) showed atrophic muscle fibres with some ragged red fibres, and a diagnosis of Kearns-Sayre syndrome was made.

At 12 years a cardiac pacemaker was inserted for Stokes-Adams attacks associated with heart block. Tetany, due to primary hypoparathyroidism, was controlled with hydroxycholecalciferal.

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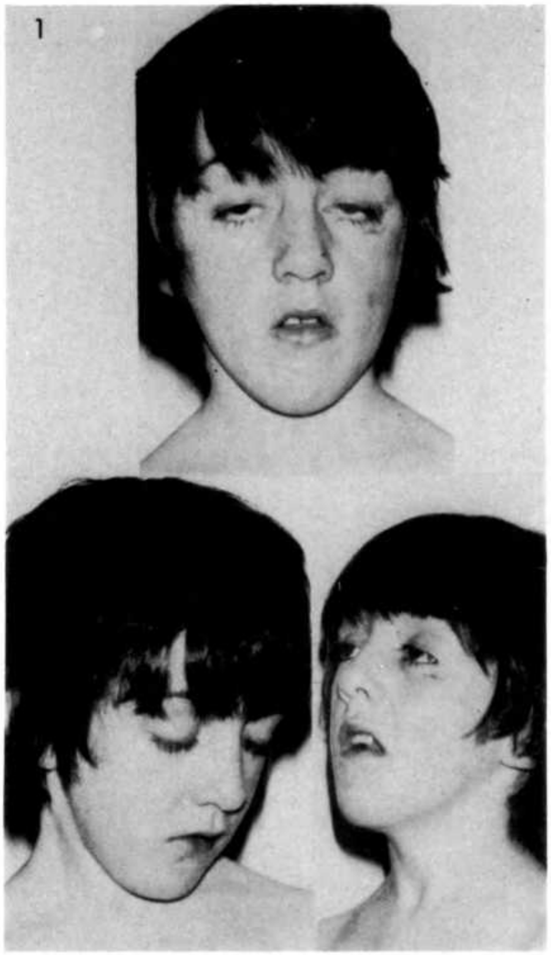

Fig. 1 *The patient one year before death.*

The boy suffered intractable cardiac failure at age 14 and died after three days at 1400 hours.

Materials and methods

The left and right eyes were obtained at necropsy. Phosphate buffered glutaraldehyde (2%) was injected into the vitreous immediately post mortem. The enucleated eyes were fixed in formal saline.

Left eye. After gross examination the left eye was processed conventionally for paraffin histology. Serial sections were cut in the horizontal plane through the pupil, the macula, and the optic nerve head.

Right eye. Twenty four tissue blocks were taken from the locations shown in Fig. 2. In addition a small central area of retinal tissue was taken for examination by scanning electron microscopy. After dissection the tissue blocks were additionally fixed in 2% glutaraldehyde buffered with 0·1 M sodium cacodylate (pH 7·2). After secondary fixation in 1% osmium tetroxide in 0·1 M sodium cacodylate buffer the tissue was dehydrated through a graded series of acetone solutions and embedded in Transmit resin prior to examination in a Phillips 301 electron microscope. The tissue for scanning electron microscopy was taken from the perimacular area (see Fig. 2) and was prepared by the critical point drying method for examination in a Jeol SEM (2B).

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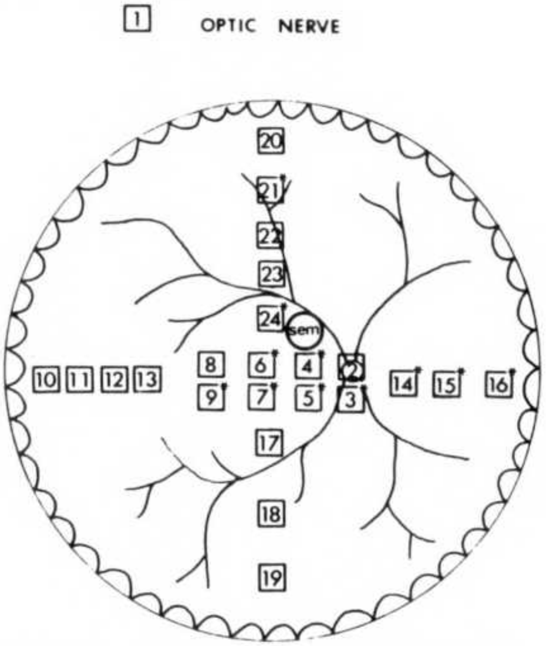


Fig. 2 *Locations in the right eye of tissue blocks taken for investigation. Block numbers correspond to those in Table 1. * Indicates that photoreceptors were found in that block.*

Semithin sections were cut from all the designated blocks. Blocks that showed interesting or unusual features were recut for electron microscopy.

Results

The left and right eyes showed similar macroscopic appearances. In addition the histology in the paraffin sections of the left eye was found to correlate well with the findings obtained in the right eye by light and electron microscopy.

Left eye (macroscopic). The anterior part of the eye was of normal appearance. At the retinal periphery there was some fine pigmentary speckling, while towards the posterior pole there was gross pallor and

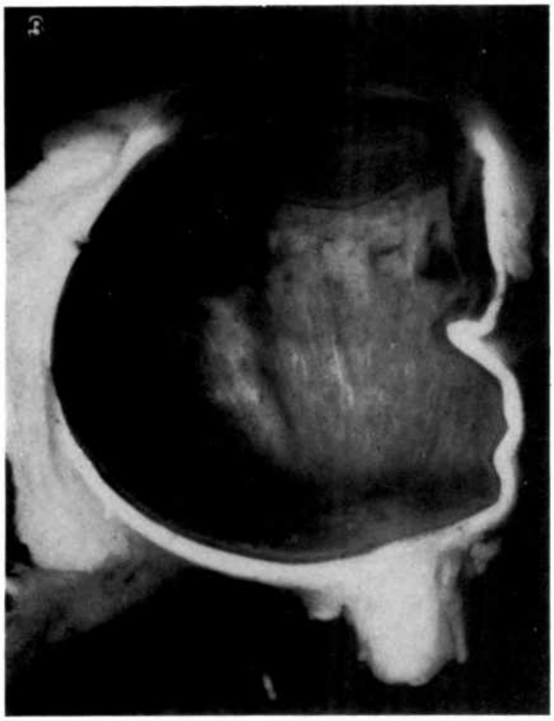


Fig. 3 *Macroscopic photograph of the left eye. Note the slight bone spicule pigmentation in the periphery and the 'salt and pepper' appearance of the more posterior fundus.*

loss of pigmentation. The optic disc was white. The retinal vessels, the choroid, and the sclera were unremarkable (Fig. 3).

Left eye (microscopic). The most significant abnormalities were observed in the outer retina. Photoreceptor cells were absent except at the posterior pole. There was, however, a peripapillary region of cell loss (Fig. 4a). In areas of photoreceptor survival retinal pigment epithelial (RPE) cells were also present. These regions of surviving pigment epithelial photoreceptor complex appeared to form discrete islands of cells that were more common toward the posterior pole (Fig. 4a, b, c, d, e). At the edge of these areas the outer limiting membrane appeared to bend inwards to fuse with the RPE and to enclose residual photoreceptors and macrophages in the subretinal space. Large pigment laden cells were often seen within such areas of preservation (Fig. 4b). Posteriorly the surviving RPE appeared to be attenuated and depleted of melanin (Fig. 4c, d, e). Where the RPE monolayer was absent, gliotic outer retina appeared to fuse directly with Bruch's membrane (Fig. 4f). In the peripheral retina there was complete atrophy of the outer retina with occasional migration of isolated pigment containing cells into the residual atrophic retinal tissue (Fig. 4g). Fluorescence microscopy failed on unstained sections to detect any lipofuscin granules in the pigment epithelium or the exogenous cells in the retina.

The optic disc and the optic nerve contained numerous axons, but in absolute numbers the impression was that there were fewer than in normal tissue of this age group. Axons were absent from the peripheral bundles of the optic nerve, though myelination appeared to be normal in the central part of the optic nerve.

Right eye (light microscopy, transmission, and scanning electron microscopy). A summary of the light microscopic findings is given in Table 1.

At the ora serrata there was marked hyperplasia of the RPE (Fig. 5a, b). Occasionally an epiretinal membrane was present (Fig. 5b). Beneath these areas of RPE hyperplasia fibrovascular proliferation was found (Fig. 5a). Blood vessels were also found beneath the pigmented epithelium but above Bruch's membrane in the region of the pars plana (Fig. 5c). At the far retinal periphery the outer nuclear layer was absent, though a few isolated pigment epithelial cells were in contact with expanded Muller cell cytoplasm (Fig. 5d). In the paramacular area the isolated regions of photoreceptors and RPE preservation were more profitably studied in semithin sections and were found to vary in size and morphological characteristics. In some segments there were recognisable monolayers of RPE with numerous photoreceptors (Fig. 5e), while in other areas circular spaces surrounded residual photoreceptors, and a few RPE cells persisted (Fig. 5f). Frequently these enclosed regions of the subretinal space contained large pigment laden cells (Fig. 5e and 5g). In the macular region the outer retina was of more normal appearance, though there appeared to be a marked reduction in the thickness of the outer nuclear layer and attenuation of the RPE cell layer (Fig. 6a). As in other regions of surviving photoreceptors cells of macrophagic character were often seen within the subretinal space (Fig. 6b).

Electron microscopy of the regions of surviving photoreceptor/RPE cell complex confirmed the presence of macrophages within the subretinal space (Figs. 7 and 8a). These macrophagic cells contained both photoreceptor cell outer segment debris and spindle shaped melanin granules that appeared to be of pigment epithelial origin.

The surviving RPE was of abnormal appearance. It lacked both apical villi and basal infoldings (Figs. 7, 8a, b) and contained no phagosomes or lipofuscin. However, a striking feature of the RPE was the presence throughout the cytoplasm of large numbers of mitochondria (Figs. 7, 8a, b, 9a, b). The distribution was quite different from the normal in which

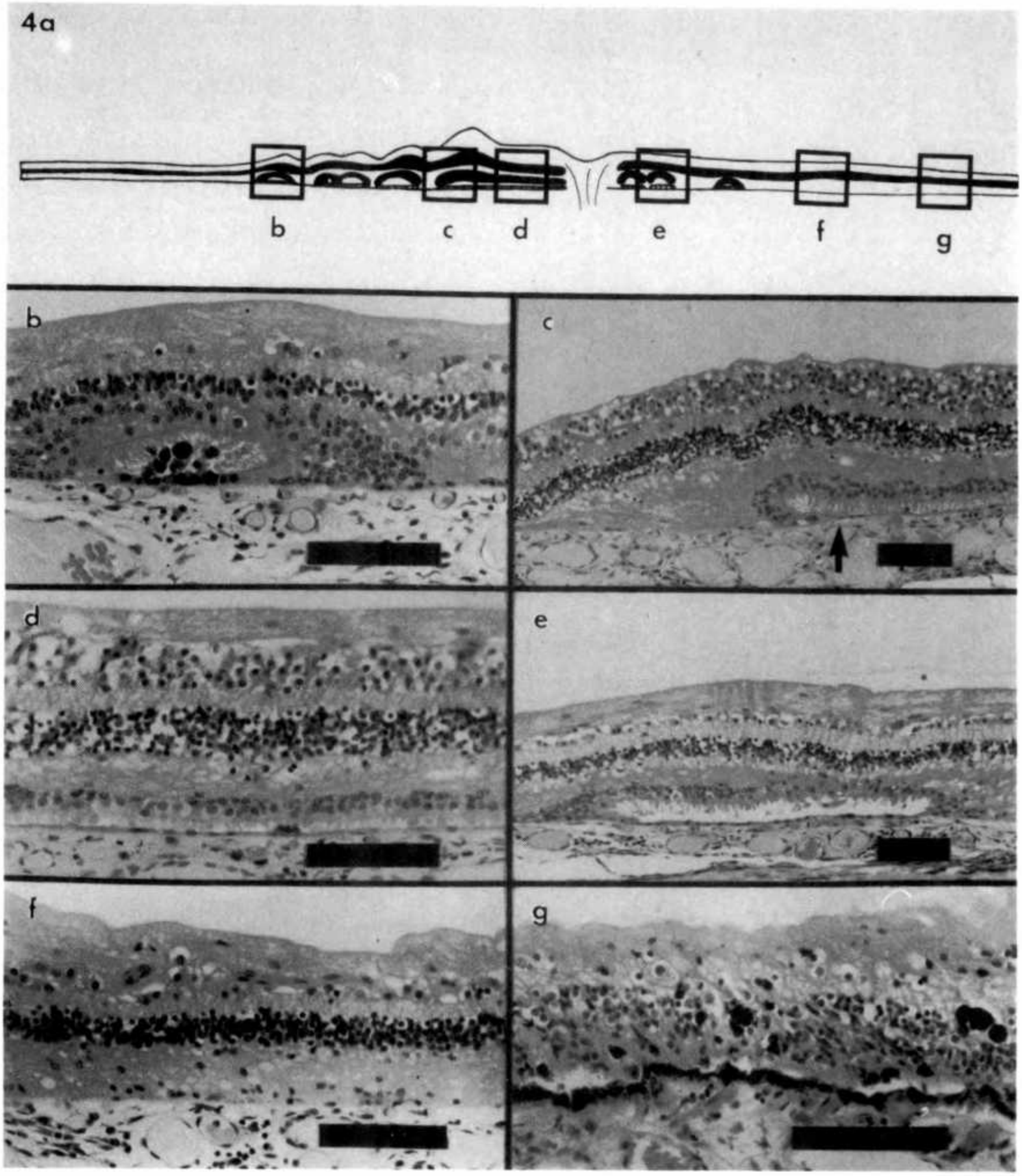


Fig. 4(a) *Distribution of the inner and outer nuclear layers (the ganglion cell layer is omitted) in the horizontal plane through the optic nerve head in the left eye. Retinal location of the following micrographs is indicated by the figure part letter.* (b) *Small island of surviving photoreceptors. Melanin containing cells are present in the subretinal space.* (c) *A more extensive region of photoreceptor cells. The RPE is markedly attenuated and terminates abruptly* (arrow). (d) *Appearance of the retina temporal to the optic nerve head. Both the RPE and the outer nuclear layer are markedly attenuated.* (e) *A region of surviving photoreceptors nasal to the optic nerve head.* (f) *Regional of nasal retina showing complete loss of photoreceptors and RPE cells.* (g) *Region of nasal peripheral retina showing complete loss of photoreceptors. Pigment containing cells are present in the retina. In all cases calibration bar = 100 µm.*

Table 1 *Summary of light microscopic findings*

Tissue block No	*Histology*	*Assessment of retinal structure*				*Comments*
		RPE	*Cones‡*	*Rods‡*	*Pigmented macrophages‖*	
1	Normal	—	—	—	—	—
2	Abnormal	Absent	Absent	Absent	Absent	Retina absent, only nerve fibre layer present
3	Abnormal	Patchy	Present*	Present*	Present SR	Numerous macrophages associated with photoreceptor outer segments
4	Abnormal	Patchy	Present†	Present†	Present SR	Macrophages numerous¶
5	Abnormal	Patchy	Present*	Present*	Present SR	—
6	Abnormal	Patchy	Present†	Present†	Present SR	—
7	Abnormal	Patchy	Present*	Present*	Present SR	—
8	Abnormal	Absent	Absent	Absent	Present	—
9	Abnormal	Patchy	Present†	Present*	Present SR NR	Small enclosed islands of photoreceptors¶
10	Abnormal	Present	Absent	Absent	Present NR	Hyperplasia of RPE at ora serrata¶
11	Abnormal	Patchy	Absent	Absent	Present NR	—¶
12	Abnormal	Patchy	Absent	Absent	Present SR NR	—
13	Abnormal	Patchy	Absent	Absent	Present NR	—
14	Abnormal	Present	Present†	Present§	Present SR	—
15	Abnormal	Absent	Present	Present†	Present NR	Small enclosed islands of photoreceptors¶
16	Abnormal	Patchy	Present	Present	Present SR NR	—
17	Abnormal	Absent	Absent	Absent	Present NR	—
18	Abnormal	Patchy	Absent	Absent	Present NR	—
19	Abnormal	Present	Absent	Absent	Absent	Capillaries below pigmented epithelium¶
20	Abnormal	Absent	Absent	Absent	Present NR	—
21	Abnormal	Patchy	Present*	Present*	Present SR NR	Small island of photoreceptors and macrophages¶
22	Abnormal	Absent	Absent	Absent	Present NR	—
23	Abnormal	Absent	Absent	Absent	Present NR	—
24	Abnormal	Present	Present*	Present*	Present SR	—

Rods and cones. Present=Cell body present; no inner or outer segments seen. Present*=Cell body and inner segment seen. Present†=Cell body and both inner and outer segments seen.

Pigmented macrophages. NR=Macrophages in neural retina. SR=Macrophages in subretinal space.

‡Receptor cells found only in association with surviving RPE cells.

§Very unusual circle of photoreceptors.

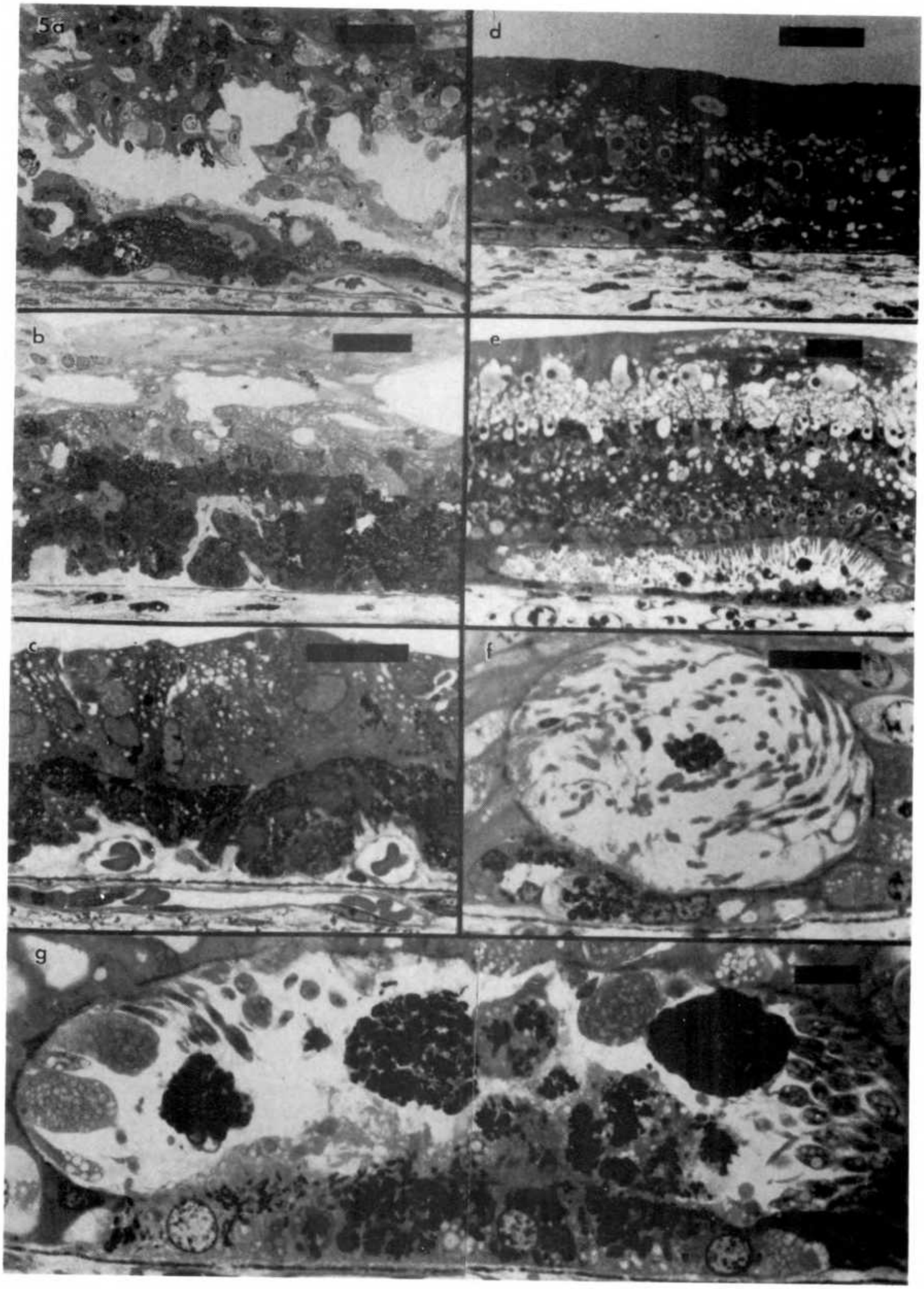
‖Macrophages described as in neural retina when RPE and photoreceptors completely absent, even though they may be in contact with Bruch's membrane.

¶Feature shown as illustration.

mitochondria are confined to the basal part of the cytoplasm. These mitochondria were in some areas very well preserved and contained plate like cristae. Bizarre mitochondria, as described in muscle fibres in some forms of the Kearns-Sayre syndrome, were not observed within the RPE monolayer, though large and irregularly shaped mitochondria were prominent (Fig. 9a, b).

Though it would have been desirable to quantify the apparent increase in the number of mitochondria per cell, this was not possible for two reasons. First, normal control material is not available. Secondly, the extreme variation in RPE cell size in the pathological material would have made a quantitative analysis extremely difficult and time consuming. Normal adult RPE cells have an approximate width of 20 μm and are 10 μm high. The RPE cells in our material were 7–10 μm high but were highly irregular in shape. Some of them were spindle shaped and measured more than 60 μm in their greatest

Fig. 5 *Composite figure showing the appearance of various retinal areas as seen by light microscopy of plastic embedded tissue.* (a) *(Table 1, block 10). Region of RPE hyperplasia at the ora serrata. Note the blood vessels between Bruch's membrane and the pigmented epithelium. Bar=40 μm.* (b) *(Table 1, block 10). A more peripheral region of the same block as shown above. An epiretinal membrane is present. Bar=40 μm.* (c) *(Table 1, block 19). Pars plana adjacent to the ora serrata. There are prominent capillaries under the pigmented epithelium. Bar=20 μm.* (d) *(Table 1, block 11). A region of complete photoreceptor cell loss. Some RPE cells are present as well as a few pigment containing cells. Bar=40 μm.* (e) *(Table 1, block 9). An island of surviving photoreceptor cells in the posterior retina. Pigment containing cells are prominent in the subretinal space. Bar=40 μm.* (f) *(Table 1, block 15). Unusual circular structure formed by curving round and down of the outer limiting membrane. Bar=20 μm.* (g) *(Table 1, block 21). A region of surviving photoreceptors in the retinal periphery. The small enclosed region of subretinal space contains numerous pigment laden cells. The RPE, while typically amelanotic, contains melanosomes in this area. Bar=10 μm.*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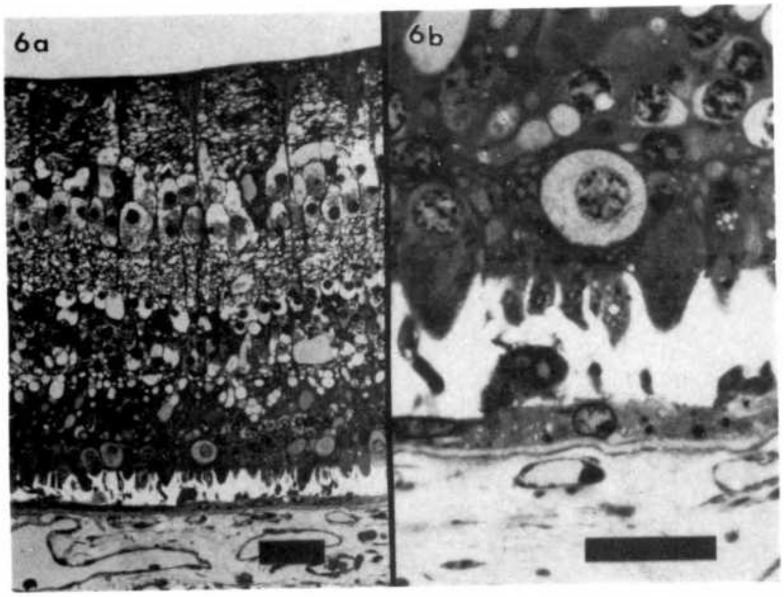

Fig. 6 *(Table 1, block 4).* (a) *A region of central retina where there is a marked reduction in the number of photoreceptor cells. Bar=40 μm.* (b) *Same area at higher magnification showing attenuation of the choriocapillaris and a cell of macrophagic appearance in the subretinal space. Bar=20 μm.*

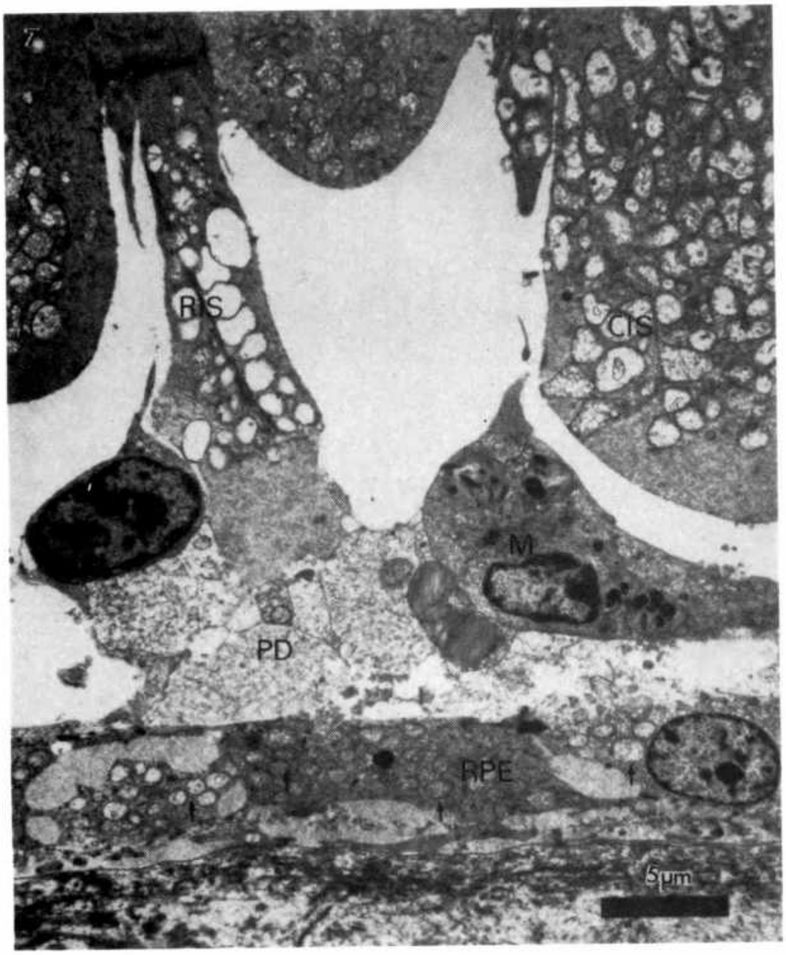

Fig. 7 *Electron micrograph showing the appearance of the photoreceptors and pigment epithelium.* M=*macrophage,* CIS=*coner inner segment,* RIS=*rod inner segment,* RPE=*retinal pigment epithelium,* PD=*photoreceptor debris, Mitochondria, shown by arrows.*

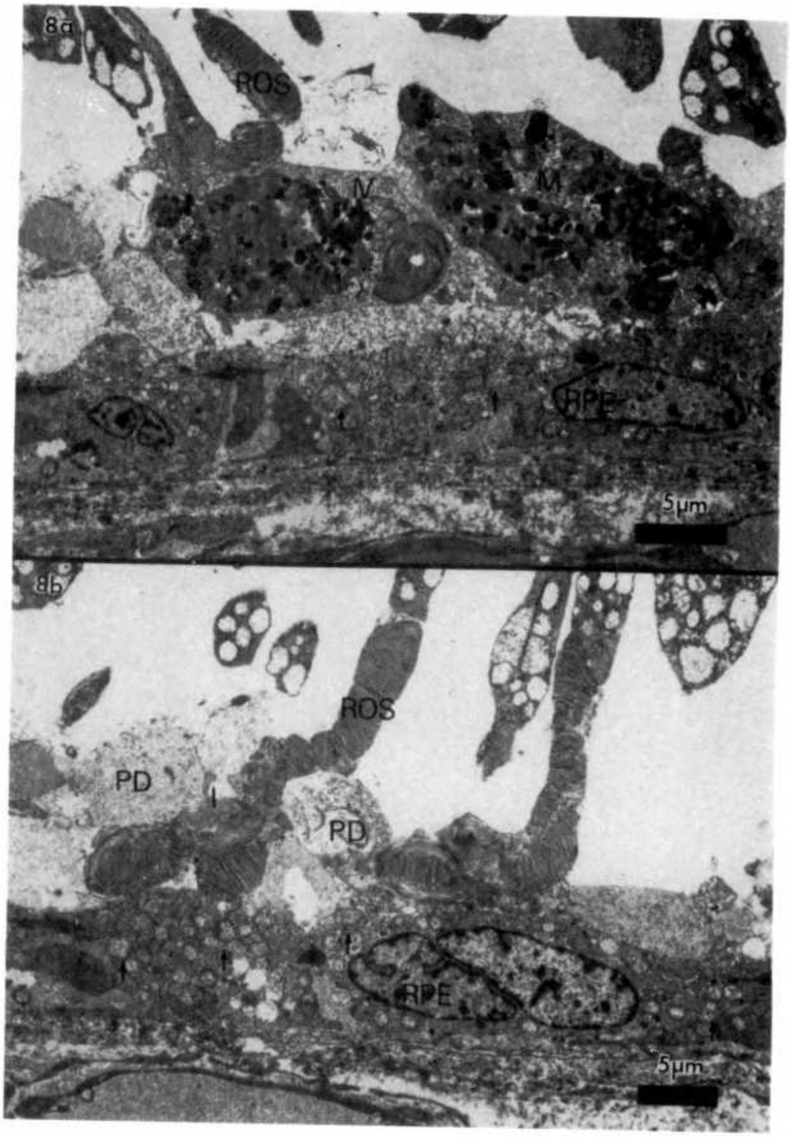

Fig. 8 *Electron micrographs showing the RPE* (a) *with pigment containing macrophages on its apical surface, and* (b) *the accumulation of outer segment material. Note the absence of apical microvilli and basal infoldings.* ROS=*rod outer segment,* M=*macrophage,* RPE=*retinal pigment epithelium,* PD=*photoreceptor debris, Mitochondria, shown by arrows.*

dimension. This difference in cell shape effectively precluded meaningful quantitation of the numbers of mitochondria per cell.

In some areas there was an accumulation of photoreceptor debris on the apical surface of the RPE cells (Fig. 8b). It was not possible to be sure in this material if the membrane bound debris represented either dislocated tips or fragments of outer segments. The important finding was that, although the rod outer segment debris was often in intimate contact with the RPE, there was no evidence of phagocytosis (Figs. 8b, 9a, b).

In all the surviving RPE cells the apical junctional complex was present (Fig. 9a, b), though some cells showed a marked elongation and convolution of the lateral cell membrane (Fig. 9b). An absence of proteinaceous material between the surviving photoreceptor outer segments suggested that in areas of surviving RPE the outer retina blood barrier was intact. Sophisticated study of tight junctions (for example, by freeze fracture) was not possible in this material. Scanning electron microscopy of the inner surface of the RPE surface suggested that the RPE cells were highly irregular in shape (Fig. 10a). This irregularity of shape probably accounted for the elongation of the lateral cell membrane seen by

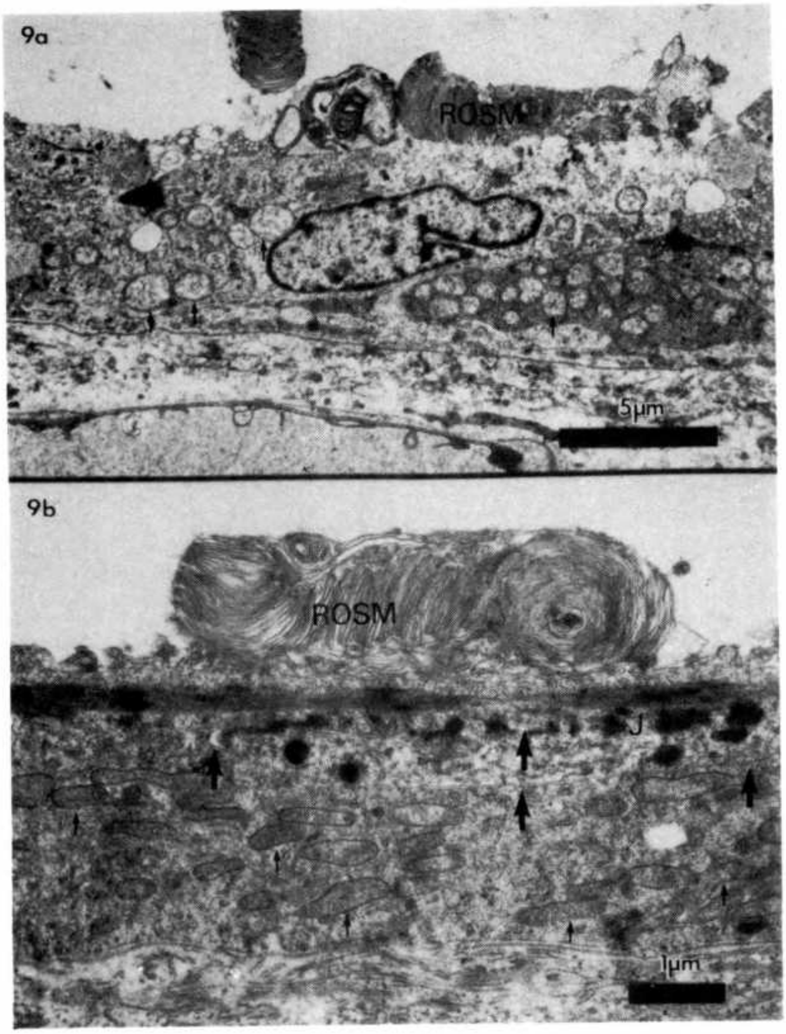

Fig. 9(a) *Electron micrograph of an RPE cell with rod outer segment material in contact with its apical surface. Thee is no indication of phagocytosis.* (b) *Similar area as above but at higher magnification. Note the numerous mitochondria and the elongated lateral cell membrane.* ROSM=*rod outer segment material,* J=*junctional complex. Mitochondria shown by arrows. Larger arrows show lateral cell membrane.*

transmission electron microscopy. By scanning electron microscopy it was frequently difficult to determine if the subretinal cells were irregular shaped intrinsic cells of the RPE monolayer or macrophagic cells in intimate contact with the surface of the underlying monolayer. Transmission electron microscopy of similar areas to those shown in Fig. 10a suggested that some of the surface cells were extrinsic to the monolayer (Fig. 10b).

Frequently cells of unknown origin were seen between the lateral cell membranes of the RPE cells (Figs. 10b, 11a, b). These cells had an appearance compatible with that of differentiating mononuclear leucocytes and were considered to be precursors of the subretinal macrophages that contained melanophagosomes and outer segment debris (Figs. 7, 8a, 10b).

Discussion

There is some controversy as to the definition of Kearns-Sayre syndrome. Drachman[9] coined the term 'ophthalmoplegia plus' to encompass the variety of neural, cardiac, and retinal disorders that may occur in conjunction with ophthalmoplegia. However, there is a consistent trend in those cases that begin in the first or second decades of life, and this is characterised by ophthalmoplegia, atypical pigmentary degenerations of the retina, and heart block. This is the clinical combination originally described by Kearns and Sayre.[1] Some authors, however, have noted other associated features such as spongy degeneration of the brain,[4] raised cerebrospinal fluid protein levels,[10] and hypoparathyroidism.[6] Hypoparathyroidism was present in the patient described here.

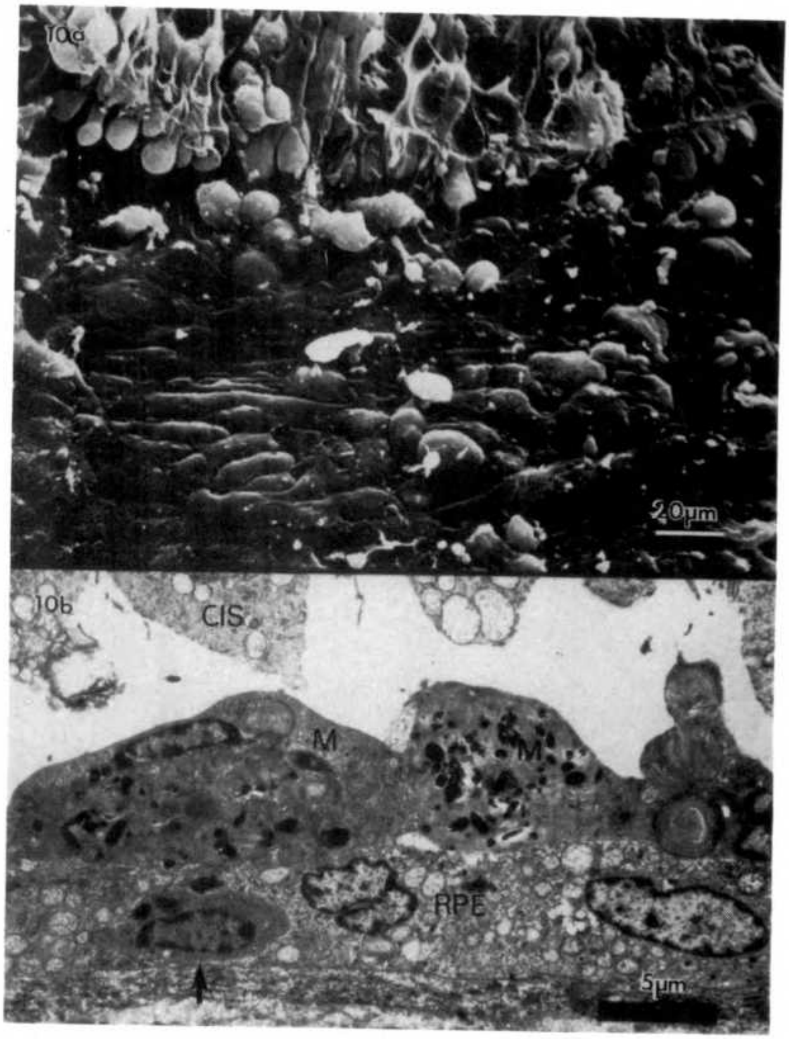

Fig. 10(a) *Scanning electron micrograph showing the apical surface of the RPE and a torn edge of the retina. Inflammatory cells are present on the surface of a highly irregular layer of RPE cells.* (b) *A similar area as seen by transmission electron microscopy. Note the small cell between the RPE cells* (arrow). CIS=*cone inner segment*, M=*macrophage*, RPE=*retinal pigment epithelium*.

In agreement with Berenberg *et al.*,[10] Bastiaensen *et al.*,[11] and François[12] we feel that the term Kearns-Sayre syndrome should be restricted to the disease of infantile onset-a multisystemic neuromuscular disease with chronic progressive external ophthalmoplegia, obligate cardiac and retinal signs, and a high protein content of the cerebrospinal fluid. It should be added that Bastiaensen *et al.*[11] have also described a juvenile form and an adult form characterised by onset in the third decade of life or later. These juvenile and adult forms are probably best classified as Kearns disease.[12] The course of all the subgroups is variable, but the severity appears to be related to the age of onset. The infantile form, the Kearns-Sayre syndrome, has the worst prognosis.

The retinopathy of Kearns-Sayre syndrome or Kearns disease is usually termed atypical to distinguish it from the more characteristic pigmentary retinopathy of the retinitis pigmentosa group of diseases. The retinal degeneration in Kearns-Sayre syndrome often occurs centrally and without a conspicuous pigmentation of the peripheral retina.[13] The fundus is more typically described as having a 'salt and pepper' or 'motheaten appearance.[13]

To the best of our knowledge there are eight reports in the literature in which the retina of Kearns-Sayre syndrome has been examined histologically, five by conventional wax histology[1-6] (Kearns reporting the same case twice[1 2]) and two by electron microscopy.[7 8] The reports that mention or illustrate the retinal histology differ considerably. Those of Kearns and Sayre[1] and Kearns[2] describe a local absence of rods and cones with an almost complete absence of the pigment epithelium. The outer

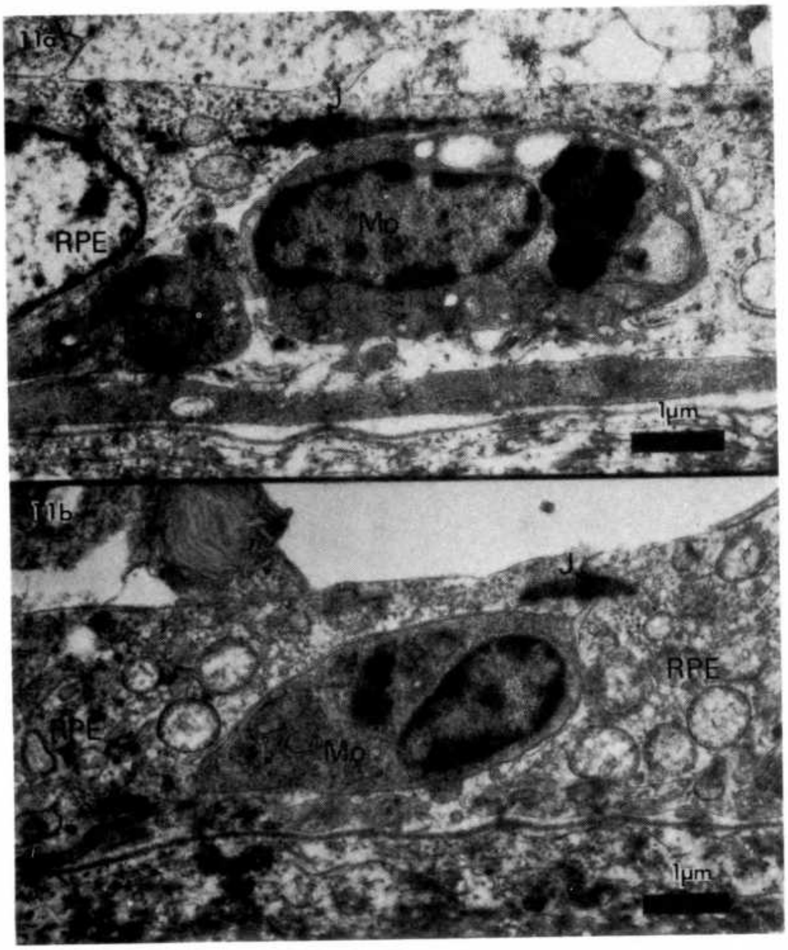

Fig. 11(a), (b) *Electron micrographs of the small cells seen between the lateral cell membranes of RPE cells. These cells are thought to be monocytes.* Mo=*monocyte,* RPE=*retinal pigment epithelium,* J=*junctional complex.*

nuclear layer was absent in areas, and much of the retina was gliotic. An essentially similar description of the retinal morphology was given by Castaigne and coworkers.[5] Horwitz and Roessmann[6] reported only a few rods at the posterior pole, while the rod and cone layer was absent elsewhere. The findings in these studies are quite similar to the findings in this study. In contrast the study of Jager *et al.*[3] reported no histological abnormality of the retina, and that of Daroff *et al.*[4] mentions only a degeneration of rods and cones.

The report of Newell and Polascik[7] describes the light and electron microscopic findings, both transmission and scanning, in the post mortem eyes of a 19-year-old. They reported the presence of enlarged mitochondria in the RPE (similar to our findings in this study), the receptor cell inner segments, and the ciliary body. They also reported the presence of large macrophages within the subretinal space. As in this study these cells were reported to contain receptor cell outer segment debris. However, they also reported ingestion of receptor cell outer segment material by the RPE. This was not observed in the present case. The only other electron microscopic study is that of Eagle *et al.*,[8] who described the findings in the eyes of a 52-year-old man. Their findings differ from those in the present case in some important respects. The photoreceptor and RPE cell loss was most marked toward the posterior pole in their material. In the present study the photoreceptor and RPE cell loss was most marked in the retinal periphery, though some loss of photoreceptors and RPE cells was evident around the optic nerve head. Eagle *et al.*[8] also reported a patchy depigmentation of the RPE with some cells containing large granules or aggregates of pigment granules. They did not report any mitochondrial abnormalities. In our material the majority of the RPE cells were devoid of melanosomes but did contain numerous, often enlarged, mitochondria. The differences between these two studies can be attributed to the age difference and a more rapid development of the disease, but the possibility of different pathogenetic processes within the spectrum of the Kearns-Sayre syndrome must also be accepted.

Abnormal mitochondria have been reported in patients with chronic progressive external ophthalmoplegia.[14] In the study of Mitsumoto *et al.*[14] the patients showing ultrastructural mitochondrial abnormalities all had characteristic ragged red fibres in biopsies of muscle. These authors found that the ultrastructural appearance of mitochondria obtained by muscle biopsy did not correlate with measured rates of respiratory function in isolated mitochondria. However, they did record an inverse relationship between morphometric mitochondrial fraction (numbers or area of mitochondria in electron micrographs) and the respiratory rate of the isolated mitochondria. These authors[14] suggest the possibility of mitochondrial proliferation in compensation for reduced efficiency. It is possible that such a compensating mechanism was operating in the RPE we studied and was responsible for the large numbers of mitochondria observed throughout the cell cytoplasm. Other authors have shown reductions in cytochrome c oxidase activity, reduced concentrations of cytochrome aa_3, and a decreased ratio of cytochrome oxidase/succinate cytochrome c reductase and defects in pyruvate metabolism in patients with chronic external ophthalmoplegia,[15 16] and defects in the mitochondrial respiratory chain located at NADH CoQ reductase and at cytochrome b in patients with mitochondrial encephalomyopathies.[17] These types of defect would all produce 'inefficient' mitochondria and again emphasise the possibilities of pathogenetic variation in the spectrum of the syndrome. Transmission electron microscopy studies of other tissues in patients with ophthalmoplegia plus and Kearns-Sayre syndrome have shown abnormal mitochondria in the cerebellum,[18 19] myocardium,[20] sweat glands,[21] and liver.[22]

The pathogenesis of Kearns-Sayre syndrome in the outer retina is difficult to establish from a single case. However, the gradation of damage, severest in the periphery and moderate at the posterior pole, probably illustrates the development of the degeneration. It could be assumed that the outer retinal degeneration seen in the later stages (peripheral retina) may be potentiated by the macrophages present within the outer retina. This point is of some interest as, regardless of primary pathology, an inflammatory process in the outer retina appears to be exacerbating the degree of outer retinal damage. This secondary inflammation of the outer retina may be of considerable consequence in retinitis pigmentosa[23] and other conditions where the outer retina is affected, such as uveitis and toxoplasmosis.[24] The potential of an autoimmune component is witnessed by the increasing interest in circulating anti-s antibodies in a variety of retinal conditions.[24]

However, the primary cause of the retinal degeneration in Kearns-Sayre syndrome remains obscure, though some speculation is possible. The role of defective RPE transport systems in the development of retinal degeneration has been stressed by Bird and Marshall.[25] We can now assume that the RPE is normally a very metabolically active cell monolayer. The numerous mitochondria adjacent to the basal infoldings and the numerous apical microvilli indicate that the RPE has a variety of transport systems, many of which must be energy dependent. Therefore any reduction in the cell's energy producing capacity will compromise the transport systems and phagocytosis, which is known to be an energy dependent phenomenon.[26] Therefore it is also likely to be reduced in an energy deficient RPE cell. We may then assume that the first stage in the receptor cell damage is due to an insufficient transport of metabolites via the RPE. The observed accumulation of photoreceptor debris in the subretinal space is interpreted as a consequence of impaired phagocytosis. It should be noted that many of the RPE cells observed in the course of this study were devoid of phagosomes, though receptor cell material was often in intimate contact with the apical surface. Thus the accumulation of photoreceptor debris in the subretinal space may have provided the antigen that induced a macrophagic response that went on to destroy the outer retina.

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References

1 Kearns TP, Sayre GP. Retinitis pigmentosa, external ophthalmoplegia and complete heart block. Unusual syndrome with histologic study in one of two cases. *Arch Ophthalmol* 1958; **60:** 280–9.

2 Kearns TP. External ophthalmoplegia, pigmentary degeneration of the retina and cardiomyopathy: a newly recognised syndrome. *Trans Am Ophthalmol Soc* 1965; **63:** 559–625.

3 Jager BV, Fred HL, Butler RB, Carnes WH. Occurrence of retinal pigmentation, ophthalmoplegia, ataxia, deafness and heart block. Report of a case with findings at autopsy. *Am J Med* 1960; **29:** 888–93.

4 Daroff RB, Solitare GB, Pincus JH, Glaser GH. Spongiform encephalopathy with chronic progressive external ophthalmoplegia mimicking ocular myopathy. *Neurology (Minneap)* 1966; **16:** 161–9.

5 Castaigne P, Lhermitte FG, Escourolle R, Chain F, Fardeau M, Hauw, JJ, Curet J, Flavigny C. Etude anatomo-clinique d'une observation d' "ophthalmoplegia plus" avec analyse des lésions nusculares, nerveuses centrales, ocularies, myocardiques et thyroidiennes. *Rev Neurol (Paris)* 1977; **133:** 369–86.

6 Horwitz SJ, Roessmann U. Kearns-Sayre syndrome with hypoparathyroidism. *Ann Neurol* 1978; **3:** 513–8.

7 Newell FW, Palascik HA. Mitochondrial disease and retinal pigmentary degeneration. In: Shimiza K, Oosterhuis J, eds. *Proceedings of the 23rd International Congress of Ophthalmology. Kyoto 1978.* Amsterdam: Excerpta Medica International Congress series No 450. 1979; 615–7.

8 Eagle RC, Hedges TR, Yanoff M. The atypical pigmentary retinopathy of Kearns-Sayre syndrome. A light and electron microscopic study. *Ophthalmology* 1982; **89:** 1433–40.

9 Drachman DA. Ophthalmoplegia plus: the neurodegenerative disorders associated with progressive external ophthalmoplegia. *Arch Neurol* 1968; **18:** 654–74.

10 Berenberg RA, Pellock JM, DiMauro S. Lumping or splitting? Ophthalmoplegia-plus or Kearns-Sayre syndrome? *Ann Neurol* 1977; **1:** 37–54.

11 Bastiaensen LAK, Notermans SLH, Ramaekers CH. Kearns syndrome or Kearns disease. Further evidence of a genuine entity in a case with uncommon features. *Ophthalmologica* 1982; **184:** 40–50.

12 François J. Metabolic tapetoretinal degenerations. *Surv Ophthalmol* 1982; **26:** 293–333.

13 Bastiaensen LAK. Pigment changes in the retina in chronic progressive external ophthalmoplegia (CPEO). *Acta Ophthalmol (Kbh)* 1978; **56** (suppl 138): 5–36.

14 Mitsumoto H, Aprille JR, Wray SDH, Nemni R, Bradley WG. Chronic progressive external ophthalmoplegia (CPEO): clinical, morphologic and biochemical studies. *Neurology (Minneap)* 1983; **33:** 452–61.

15 Johnson MA, Turnbull DM, Dick DJ, Sherratt HSA. A partial deficiency of cytochrome c oxidase in chronic progressive external ophthalmoplegia. *J Neurol Sci* 1983; **60:** 31–53.

16 Rieske-Nielsen E, Lou HC, Lowes M. Progressive external ophthalmoplegia. Evidence for a generalised mitochondrial disease with a defect in pyruvate metabolism. *Acta Ophthalmol (Kbh)* 1975; **54:** 553–73.

17 Morgan-Hughes JA, Hayes DJ, Clark JB. Mitochondrial encephalomyopathies. Biochemical studies in two cases revealing defects in the respiratory chain. *Brain* 1982; **105:** 553–82.

18 Adachi M, Torll J, Volk BW, Briet D, Wolintz A, Schneck L. Electron microscopic and enzyme histochemical studies of cerebellum, ocular and skeletal muscles in chronic progressive ophthalmoplegia with cerebellar ataxia. *Acta Neuropathol (Berl)* 1973; **23:** 300–12.

19 Schneck L, Adachi M, Briet D, Wolintz A, Volk BW. Ophthalmoplegia plus with morphological and chemical studies of cerebellar and muscle tissues. *J Neurol Sci* 1973; **19:** 37–44.

20 Harati Y, Patten B, Sheehan M, Judge D, Worth J. Cardiac biopsy in Kearns-Sayre syndrome. In: den Hartog Jager W, Bryn G, Heijstee A, eds. *Abstracts of the Eleventh World Congress of Neurology, Amsterdam 1977.* Amsterdam: Excerpta Medica International Congress series 427 1978: 318.

21 Karpati G, Carpenter S, Larbrisseau A, Lafontaine R. The kearns-Shy syndrome. A multisystem disease with mitochondrial abnormality demonstrated in skeletal muscle and skin. *J Neurol Sci* 1973; **19:** 133–51.

22 Gonatas NK, Evangelista I, Martin J. A generalised disorder of nervous system, skeletal muscle and heart resembling Refsum's disease and Hurler's syndrome. II Ultrastructure. *Am J Med* 1967; **42:** 169–78.

23 Brinkman CJJ, Pinckers AJLG, Broekhuyse RM. Immune reactivity to different retinal antigens in patients suffering from retinitis pigmentosa. *Invest Ophthalmol Visual Sci* 1980; **19:** 743–50.

24 Corwin JM, Weiter JJ. Immunology of chorioretinal disorders. *Surv Ophthalmol* 1981; **25:** 287–305.

25 Bird AC, Marshall J. Retinal receptor disorders without known metabolic abnormalities. In: Garner A, Klintworth G, eds. *Pathobiology of ocular disease.* New York: Dekker, 1982; 1167–220.

26 Silverstein SC, Steinman RH, Cohn ZA. Endocytosis. *Ann Rev Biochem.* 1977; **46:** 669–722.

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Correspondence

Familial exudative vitreoretinopathy

Sir, Chaudhuri *et al.* reported abnormal platelet aggregation in patients with familial exudative vitreoretinopathy (FEVR) from two separate pedigrees.[1]

Incontinentia pigmenti is a rare skin disorder which is occasionally associated with proliferative retinopathy. The active retinal lesions of incontinentia pigmenti closely resemble those of FEVR.[2] Recently one of us (G.A.G.) saw a 13-week-old child with biopsy-proved incontinentia pigmenti. The far temporal retina in each eye was avascular. There were preretinal 'sea-fan' type vasoproliferative lesions posterior to the demarcation line between vascularised and non-vascularised retina in both eyes. Platelet function studies were carried out on this child and compared with results from a healthy 6-month-old boy with a blocked nasolacrimal duct. Platelet aggregation to added arachidonic acid (1·5 mg/ml), adrenaline (10 µM), collagen (0·5 mg/100 ml) and ADP (3 µM) showed no difference between the patient and control. Platelet thromboxane synthesis was determined in triplicate after stimulation with arachidonic acid (1·8 mM).[3] The rates of thromboxane synthesis were similar for both the patient and control (patient 5697±396 pg/min/10^7 platelets (mean±SE), control 5042±158). The work of Chaudhuri *et al.* remains to be confirmed in other patients with FEVR. Our study suggests that an underlying disorder of platelet thromboxane metabolism is not responsible for the abnormal retinal vascularisation in incontinentia pigmenti.

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References

1 Chaudhuri PR, Rosenthal AB, Goulstine DB, Rowlands D, Mitchell VE. Familial exudative vitreoretinopathy associated with familial thrombocytopathy. *Br J Ophthalmol* 1983; **67**: 755–8.
2 Van Nouhuys CE. Dominant exudative vitreoretinopathy and other vascular developmental disorders of the peripheral retina. The Hague: Junk, 1982: 282.
3 Ford WDA, James MJ, Walsh JA. Congenital diaphragmatic hernia: association between pulmonary resistance and plasma thromboxane concentrations. *Arch Dis Child* 1984; **59**: 143–6.

Book review

YAG Laser Ophthalmic Microsurgery. By Stephen L. Trokel. Pp. 209. £41·40. Appleton-Century-Crofts: Norwalk, Connecticut. 1983.

This book is an excellent introduction to YAG (yttrium-aluminium-garnet) laser usage. It is essential reading for anyone embarking on the complexity and difficulties of this form of therapy. The book outlines in detail the YAG physics, the interaction of YAG pulses with ocular tissue, safety with the instrument and its clinical uses, and the possible complications of treatment with it. Although the subject is young and many of the lasers and techniques are undergoing modification, this book is recommended reading for any student of lasers.

A M PETER HAMILTON

Notes

International conference on Behçet's disease

A multidisciplinary international conference on Behçet's disease will be held under the auspices of the Royal Society of Medicine in London on 5–6 September 1985. It is hoped that there will be international participation from specialists of many disciplines to review recent advances in the understanding of the aetiology, pathogenesis, clinical manifestations, and treatment of this intractable multisystem disease. Further information from Miss M Mitchell, Royal Society of Medicine, 1 Wimpole Street, London W1.

Immunology and the eye

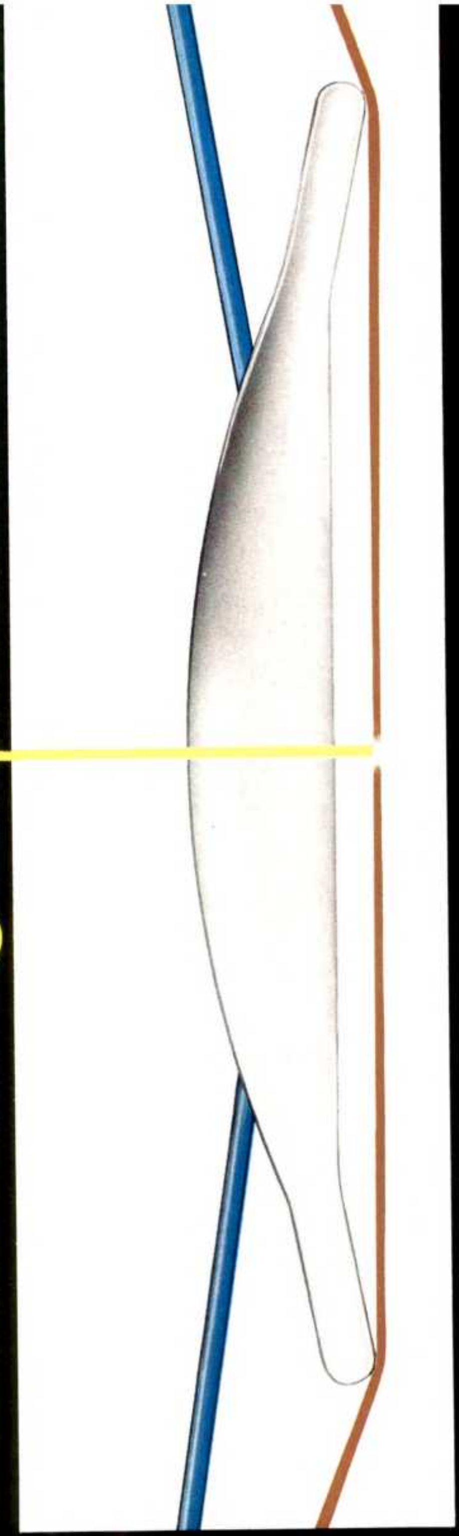
The 4th International Symposium on the Immunology and Immunopathology of the Eye will take place in Padova, Italy, on 2–4 May 1986. The main topics will include: autoimmunity, immunoregulation, vasculitis and ocular inflammation, immunology of infections, hormones in immunopathology, soluble mediators of inflammation, and general ocular immunology. The deadline for abstracts is 31 August 1985. Details from Dr Iva A. Fregona, c/o Clinica Oculistica dell'Università di Padova, Via Giustiniani 2, 35128 Padova, Italy.

Training in research

The Dana Center for Preventive Ophthalmology (ICEPO) has received a grant from the Eleanor Naylor Dana Trust for the training of highly motivated ophthalmologists in the techniques of clinical research and preventive ophthalmology. Fellowships are for one to three years and provide a basic living allowance as well as tuition for relevant course or degree work at the Johns Hopkins School of Hygiene and Public Health. Details from Training Coordinator, ICEPO, Dana Center for Preventive Ophthalmology, Wilmer Institute, Room 120, Johns Hopkins Hospital, 600 N Wolfe Street, Baltimore, MD 21205, USA.

Oculoplastic congress

The 12th International Oculoplastic Society Congress will be held on 17–24 February 1985 as a Virgin Islands air/sea yacht cruise. Details from Ms Janet Shaw, c/o Pierre Guibor, MD, 630 Park Avenue, New York, NY 10021, USA.



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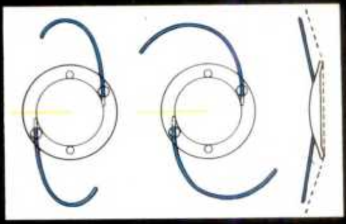

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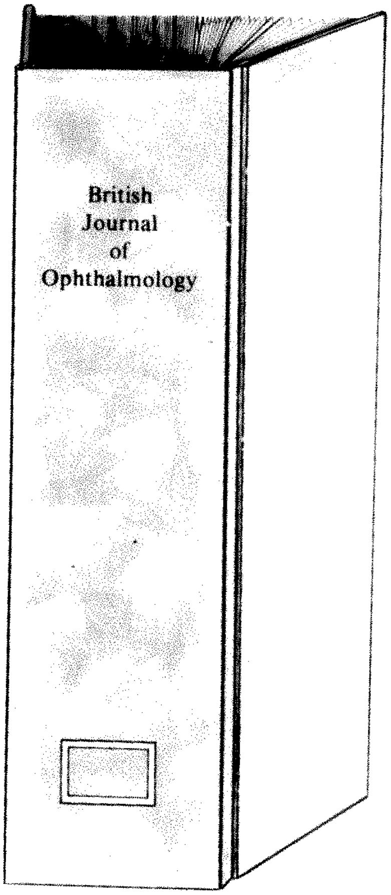

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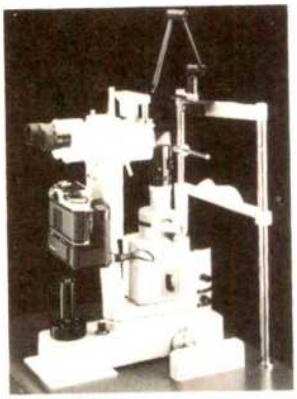

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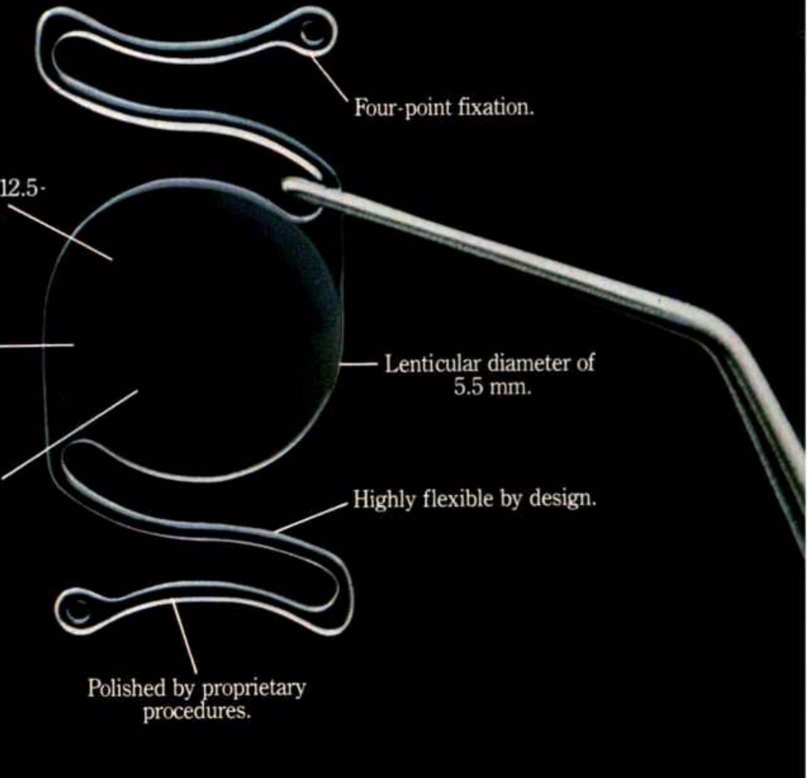

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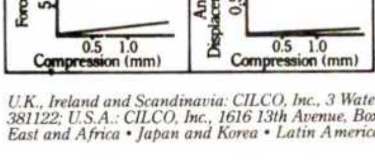

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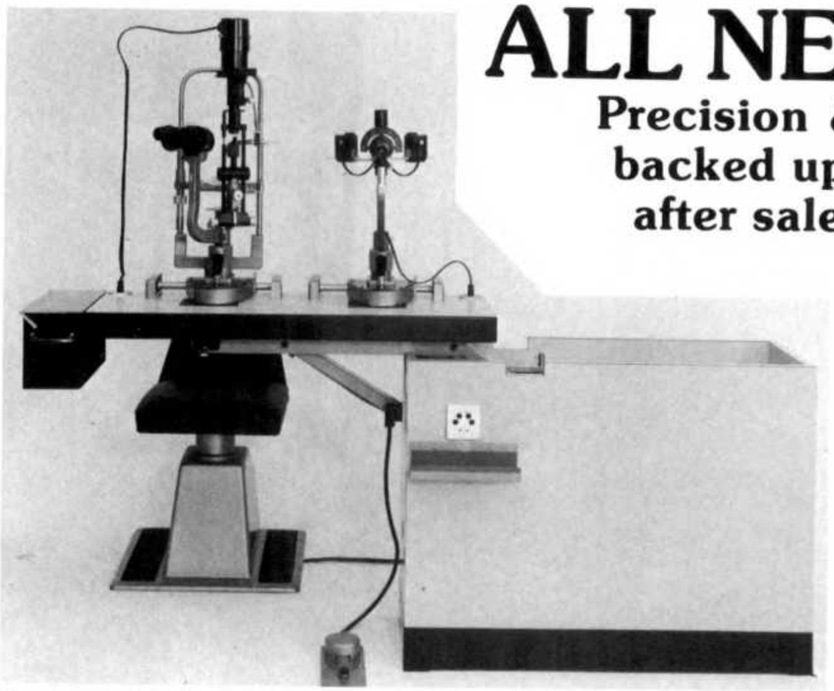

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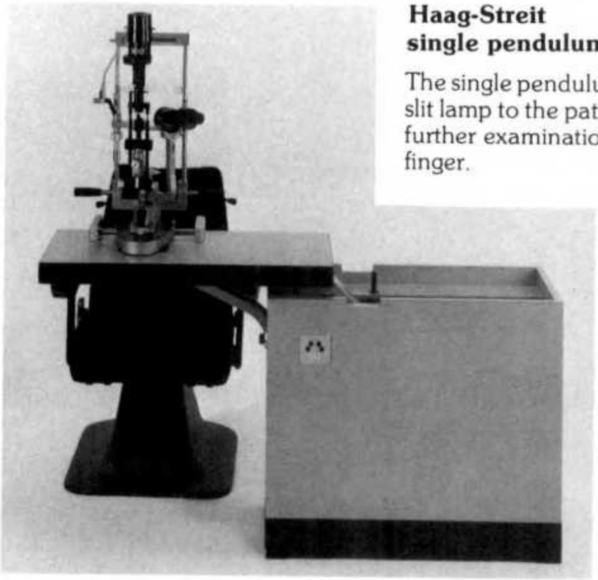

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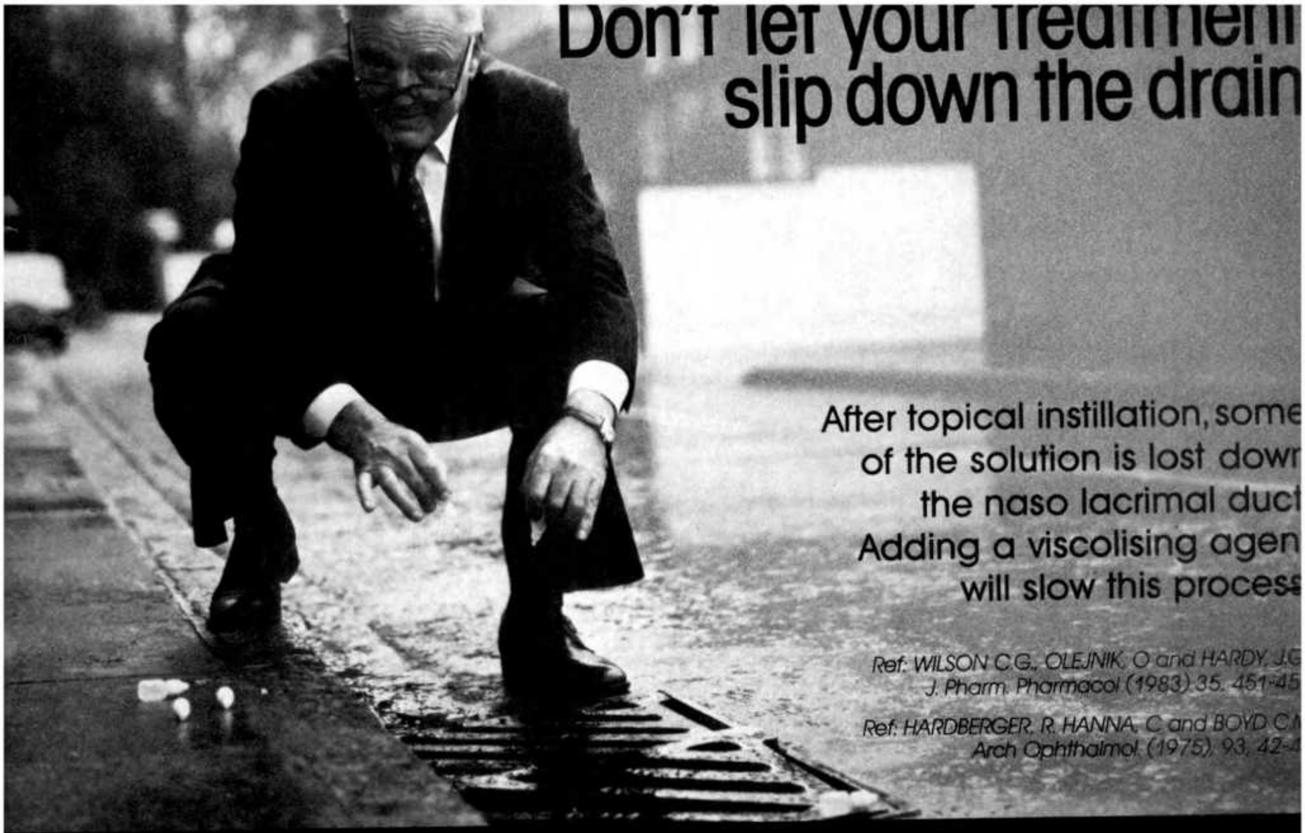

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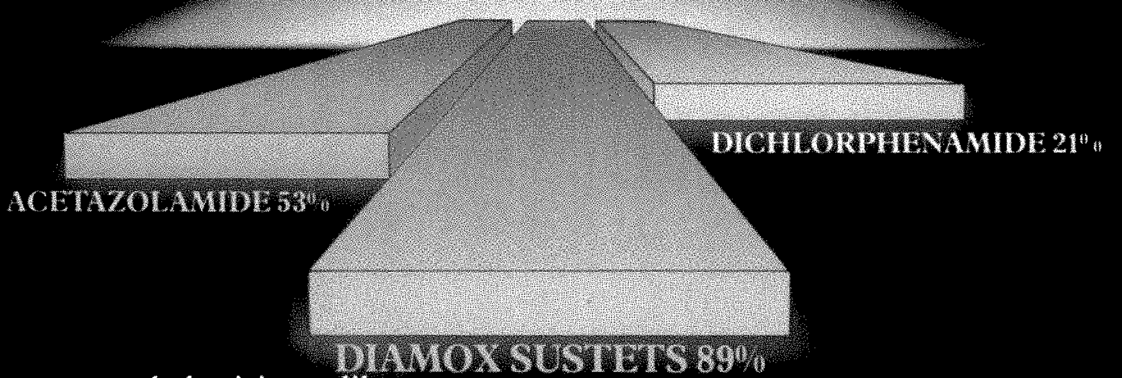

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British Journal of Ophthalmology, 1985, **69**, 77–85

Damage to the corneal endothelium during Nd/YAG photodisruption

M G KERR MUIR AND E S SHERRARD

From the Pocklington Eye Transplant Research Unit, Institute of Ophthalmology, Moorfields Eye Hospital, London

SUMMARY Damage to the human corneal endothelium, as seen by specular microscopy, associated with short pulsed neodymium: yttrium-aluminium-garnet (Nd/YAG) laser iridotomy and capsulotomy, is described. A specular and scanning electron microscopical study of fresh in vitro rabbit eyes submitted to Nd/YAG iridotomy was performed to investigate the nature of the endothelial damage. The majority of lesions showed irreversible changes ranging from individual cell destruction to disruption of large areas of the endothelium, while cells adjacent to these lesions had changes of an apparently reversible nature. It was possible to correlate accurately these scanning electron microscopic changes with the appearances seen with the clinical specular microscope. The extent of such damage appears to be related to the quantity of power delivered, its delivery mode, the number of laser bursts, and the target tissue/endothelium distance. The possible causes for such damage are discussed.

The recent introduction of short pulsed (Q-switched) Nd/YAG laser photodisruptors into clinical practice has been welcomed because of the facility for non-invasive division of transparent or opaque tissues occluding the visual axis, for creating iridotomies in the management of certain forms of glaucoma, for the division of vitreous membranes, and for preparatory anterior capsulotomies of the lens.[1-4]

Obvious advantages are that there is no surgical entry into the eye or need for a general anaesthetic, and there is therefore less demand on operating theatre time. Furthermore the laser technique is appropriate for either inpatient treatment or as an entirely outpatient service. The reported disadvantages relate to radiation and shock wave damage to structures in the vicinity of the laser focus, that is, to the crystalline lens during iridotomy, to an intraocular lens implant, and the anterior vitreous face (with the potential for increasing the likelihood of cystoid macular oedema) during capsulotomy, and to retinal photoreceptor and pigment epithelial cell damage during photodisruption of vitreous membranes.[5-8] A further disadvantage is the rise in intraocular pressure that sometimes follows iridotomy or capsulotomy. This is of particular importance because of the risk of further axonal loss in glaucomatous eyes with antecedent optic nerve damage.

There are a few reports of corneal damage. A transient corneal haze overlying the site of iridotomies in narrow-angled chambers has been described in man[1] and in other primates.[9] A Q-switched ruby laser was used for the latter.

Puliafito and Steinert[10] in a scanning electron microscopical study of rabbit eyes after anterior capsulotomy found no change in the morphology or density of the endothelial cells either in the passage of the laser beam or elsewhere, while an endothelial specular microscopical study in man by Aron-Rosa revealed no changes following capsulotomy.[3 4]

When the short pulsed (Q-switched) Nd/YAG laser came into clinical use at this hospital two slit-lamp features after both posterior capsulotomy and iridotomy were noted. First, the particulate disruption of target tissue which dispersed throughout the anterior chamber immediately following optical breakdown (vide infra). The particles were often in static suspension and returned to normal aqueous flow patterns within 1–60 minutes; second, the appearance of widely distributed clusters of sharply demarcated, non-reflecting areas within the specular image of the endothelium.

These findings prompted the present preliminary

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study which is aimed at elucidating the incidence and nature of Nd/YAG laser photodisruptor induced damage to the human corneal endothelium by specular microscopy and by the correlation of these findings with the specular and scanning electron microscopical appearances of in vitro rabbit endothelium after Nd/YAG iridotomy.

Materials and methods

The short pulsed, Q-switched Nd/YAG laser photodisruptor used in this study was a Lasag Sirius Microruptor II.

Human study. Patients had been preselected for Nd/YAG laser treatment by the referring clinician. Fifteen of the 16 eyes that had laser iridotomy were being treated for chronic narrow angle glaucoma, resolving acute narrow angle glaucoma, or as prophylaxis in the fellow eye after an acute narrow angle attack. One patient had laser treatment for marked iris bombé with extensive iridocorneal contact. Of the eight capsulotomies two had posterior chamber intraocular lens implants, two had had previous lens aspiration for congenital cataract, while the remainder had opaque capsules following extracapsular cataract surgery. Prior to Nd/YAG treatment the corneal endothelium was examined and photographed, centrally and in all four quadrants, with the Pocklington specular microscope (PSM).[11] Immediately after laser treatment a slit-lamp examination of the anterior segment was followed by further endothelial specular photomicroscopy (ESP). In some patients ESP was repeated over several days to monitor the evolution of the YAG induced changes. The laser treatment modalities are shown in Tables 1 and 2.

Animal study. Each of four fresh in vitro Dutch rabbit eyes had three full thickness Nd/YAG iridotomies with single bursts of three pulses delivering 3 mJ of energy in multimode operation.

Table 1 *Nd/YAG iridotomy laser modalities*

No	*Mode*	*Bursts*	*Pulses per burst*	*mJ*
1	MM	3	4	3·1 (×1)/5·8 (×2)
2	MM	20	NA	5·0
3	MM	1	3	8·3
4	MM	3	4	3·1
5	MM	2	4	4·5
6	MM	2	2	12·0 (×1)/5·4 (×1)
7	MM	3	2	6·4
8	MM	2	3	6·0
9	MM	2	4	8·0
10	MM	1	4	8·5
11	NA	2	NA	1·02
12	FM	1	4	4·9
13	FM	1	4	5·6
14	FM	2	4	5·3
15	FM	2	4	4·6 (×1)/5·7 (×1)
16	FM	4	1	2·0

MM=multimode, FM=fundamental mode, NA=not available.

Table 2 *Nd/YAG capsulotomy laser modalities*

No	*Mode*	*Bursts*	*Pulses per burst*	*mJ*
1	FM	3	3	1
2	FM	2	NA	3·0
3*	NA	NA	1	3·0
4	FM	20	3	3·5
5	FM	6	3	3·1
6	FM	15	3	1·0
7	FM	40	4	1·4
8*	FM	2	1	0·9

FM=fundamental mode, MM=multimode, *intraocular lens in situ, NA=not available.

ESP was done immediately before and after the iridotomies, and then the cornea was prepared for

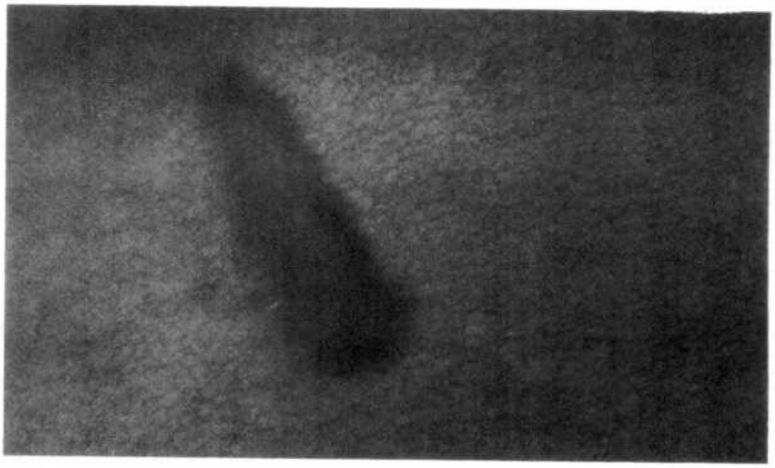

Fig. 1 *Specular photomicrograph of the in vivo corneal endothelium of an 11-year-old boy four years after congenital cataract surgery.*

Fig. 1A *Pre-YAG capsulotomy. Large dark area=KP–relocation marker. (×12).*

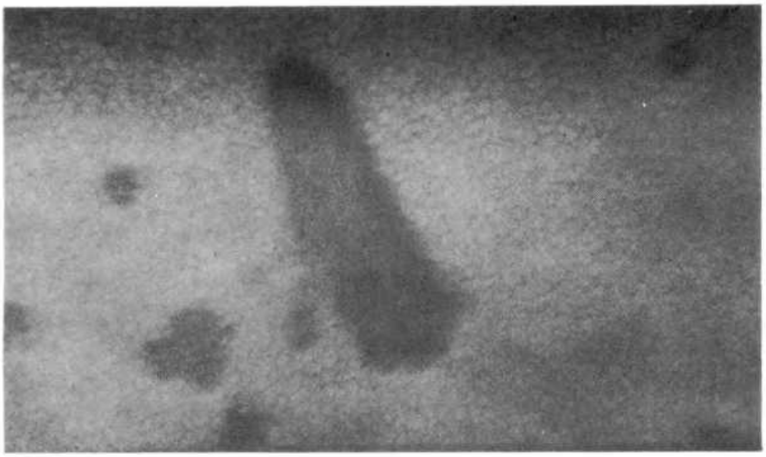

Fig. 1B *Same area as in 1A immediately after YAG capsulotomy. Additional dark areas = YAG induced lesions. (×12).*

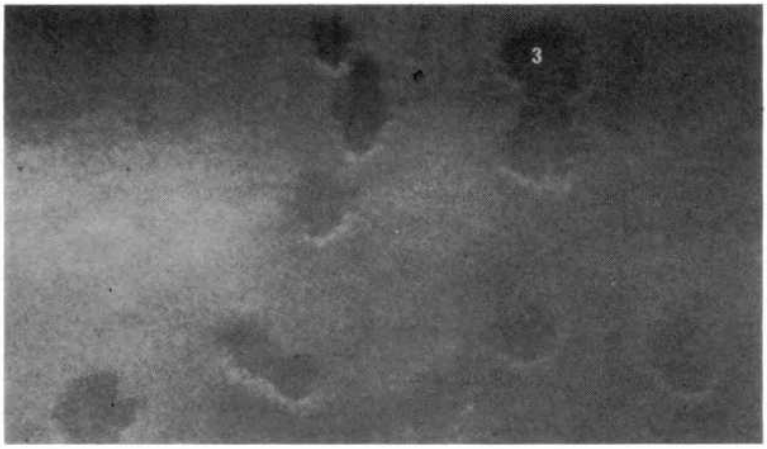

Fig. 1C *Different area of same endothelium as in 1A, see Fig. 1E (3) for location. Note bright margins. (×12).*

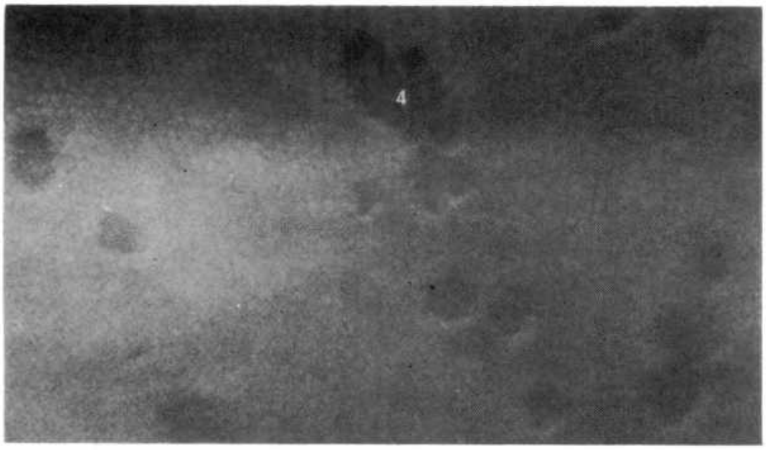

Fig. 1D *Another area of same endothelium as in 1A see Fig. 1E (4) for location. (×12).*

scanning electron microscopy (SEM) as detailed elsewhere.[12]

Results

Human studies. Specular photomicroscopy of the corneal endothelium in all cases before Nd/YAG treatment showed normal or enlarged cells. The degree of enlargement was attributable to and correlated with the previous ocular disorder such as surgery, trauma, or glaucoma.

After eight YAG capsulotomies the six without an intraocular lens implant all showed changes in the specular image of the corneal endothelium. These were mainly axial in distribution with a wide dispersal into all quadrants.

The example shown is from an 11-year-old boy who had posterior capsular remnants after congenital cataract surgery four years previously. Before YAG capsulotomy (Fig. 1A) the endothelium had a pre-existing axial feature (keratic precipitate) which served as a useful landmark for relocation after laser treatment, when the same feature was seen to be surrounded by multiple 'punched-out' lesions with scalloped borders (Fig. 1B). Similar lesions involved all four quadrants. Fig. 1E is a tracing from a montage of specular photomicrographs which shows the distribution of some of the lesions around the relocation landmark. They occurred either singly or in clusters and often showed a linear pattern. They had distinctive features (Figs. 1C, 1D). They appeared as multiple well delineated dark areas with, in most cases, a margin of brightly reflecting cells whose inner border was scalloped by a darker zone. The centre of the lesions showed some variation with from one to several black featureless circular zones, to a grey amorphous or finely speckled pattern, and the surrounding area was usually grey.

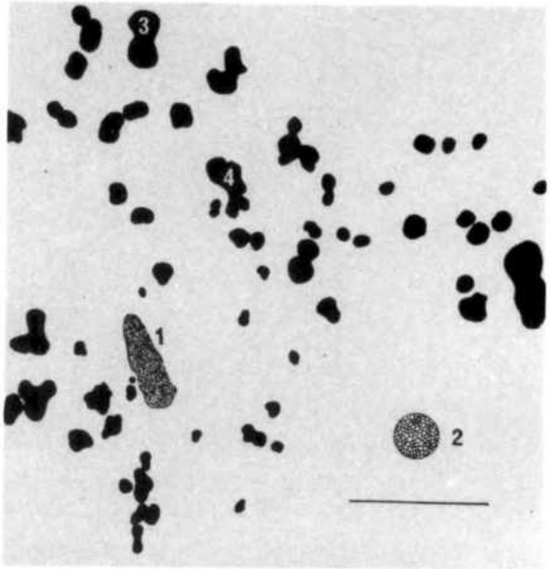

Fig. 1E *Tracing of YAG induced lesions from montage of specular photomicrographs (6 frames) illustrating their distribution. 11-year-old boy; YAG capsulotomy: 40 bursts/4 pulses per burst/1·4 mJ. Same case as Fig. 1. 1=relocation marker (see Fig. 1A, B). 2=Tracing from same endothelium at same scale, (136 cells). 3=Lesion identified in Fig. 1C. 4=Lesion identified in Fig. 1D. Bar=0·5 mm.*

Of the two capsulotomies in the presence of a posterior chamber intraocular lens implant, the endothelium, with a reduced cell population before YAG treatment, showed in one a single non-reflecting area in the inferior periphery by slit-lamp examination. However, no lesions were found with the PSM. The other had a single YAG lesion in the superior corneal periphery which was seen with the PSM.

After Nd/YAG laser iridotomy all of the 16 eyes studied showed lesions in the specular image of the

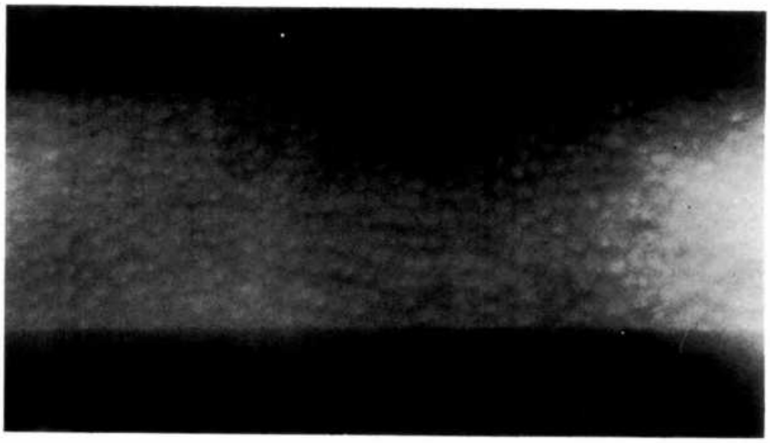

Fig. 2 *Specular photomicrograph of in vivo corneal endothelium. 24-year-old woman with iris bombé nine months after lensectomy for traumatic cataract.*

Fig. 2A *Central endothelium before iridotomy. Cells are enlarged. (×12).*

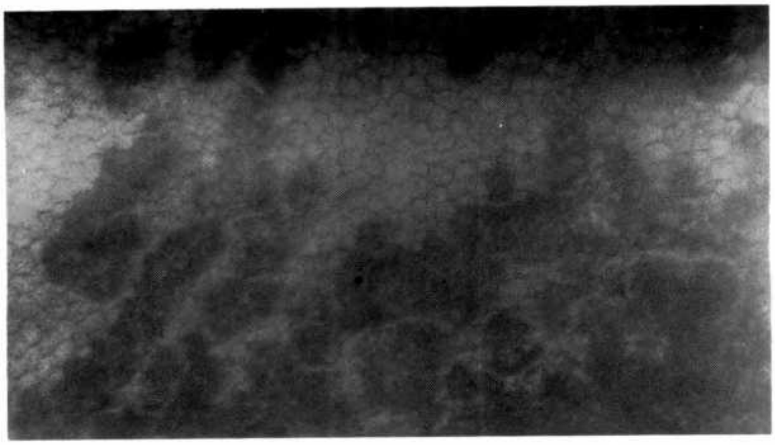

Fig. 2B *After YAG treatment. Portion of upper margin of central confluent lesions. (×12).*

Fig. 2C *After YAG treatment. Portion of lower margin of central confluent lesions. (×12). Note: Differential cell size in* B *and* C *was evident before laser treatment.*

endothelium whose appearance was identical to those induced by capsulotomy. These were concentrated in the quadrant of the iridotomy, but in the majority of cases they were distributed in other quadrants also. The example shown (Fig. 2) is from the patient with iris bombé with extensive iridocorneal contact, in whom the target tissue/endothelium distance was 1·5 mm. Fig. 2A shows the endothelium, with enlarged cells, before laser treatment. After laser treatment a large area of confluent lesions was seen in the axial region. A portion of the upper margin is shown in Fig. 2B and the lower margin in Fig. 2C. One hour after treatment the axial cornea had thickened by 0·1 mm. This extensive damage occurred in an endothelium with an already depleted cell population (Fig. 2A).

Repeated ESP of four eyes over several days showed normal adjacent endothelium spreading into the area of YAG induced damage.

Target tissue particles were dispersed throughout the anterior chamber in all cases with a greater concentration after the iridotomies, when they were associated with a turbid aqueous humour.

Animal studies. A particular feature of rabbit corneal endothelium is the presence of occasional giant cells (Fig. 3A). These serve as excellent markers for the relocation of exact areas of the endothelium and allow precise cell to cell correlation of specular photomicrographs taken before and after YAG laser iridotomy. Furthermore they permit cell to cell correlation in specular and scanning electron photomicrographs.[12]

Fig. 3A is a specular photomicrograph of normal in vitro rabbit endothelium. Scanning with the PSM revealed no abnormal features, and the giant cells in the centre of the field were selected as relocation markers. Fig. 3B shows the same giant cells relocated by scanning electron microscopy. Fig. 3C is the same endothelium, as identified by the giant cells, after YAG iridotomy, and it now shows several 'dark' YAG induced changes.

A specular photomicrograph of a typical YAG

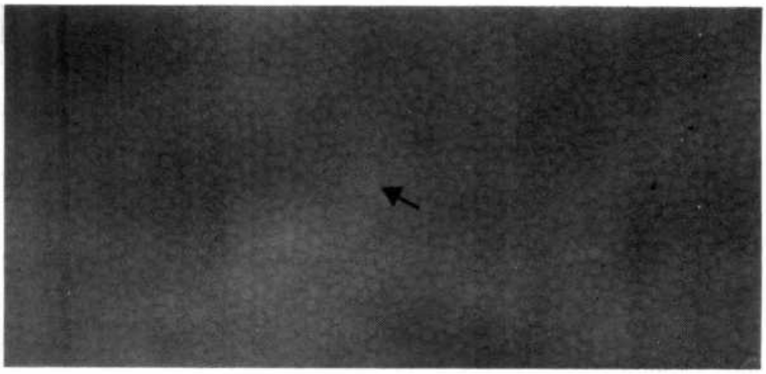

Fig. 3 *Specular and scanning electron micrograph of in vitro rabbit endothelium.*
Fig. 3A *Specular photomicrograph before laser iridotomy. The endothelium is normal and shows typical giant cells, one of which, arrowed, was centred for later relocation. (×12).*

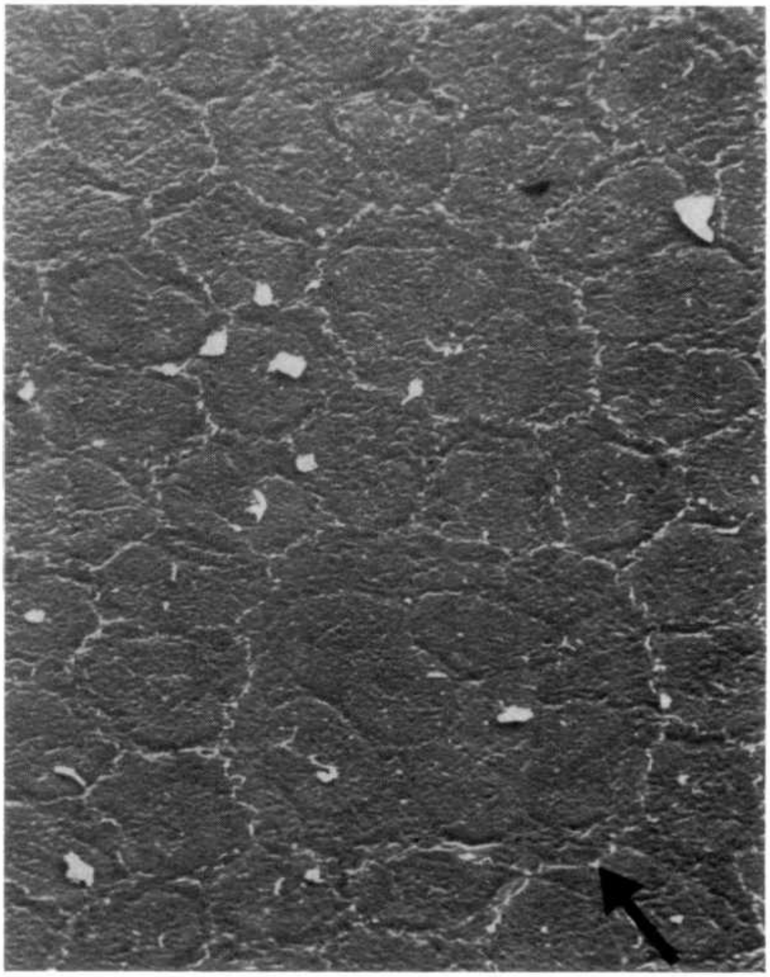

Fig. 3B *Scanning electron micrograph of portion of endothelium in 1A including the same giant cell (arrowed) at same orientation. (×870).*

induced lesion is seen in Fig. 3C. The open arrows indicate black featureless areas that are surrounded by an amorphous or finely speckled grey band, which gives way at the periphery to a narrow dark zone that abuts adjacent recognisable endothelial cells, which, however, appear compressed or scalloped and give

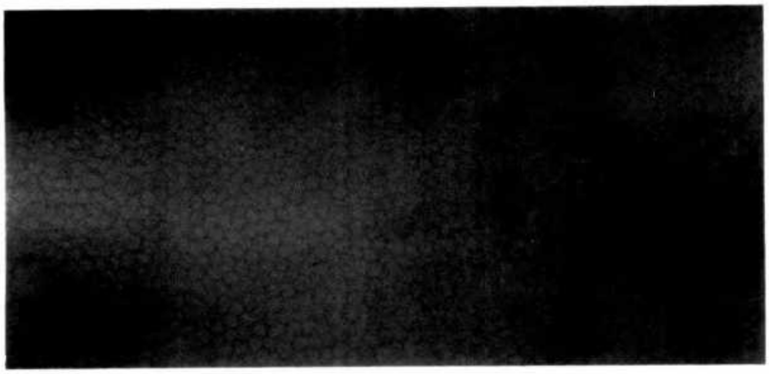

Fig. 3C *Specular photomicrograph after laser iridotomy. The field to the right of the marker giant cell now includes several YAG induced lesions. Open arrows = open arrows in 3D. (×12).*

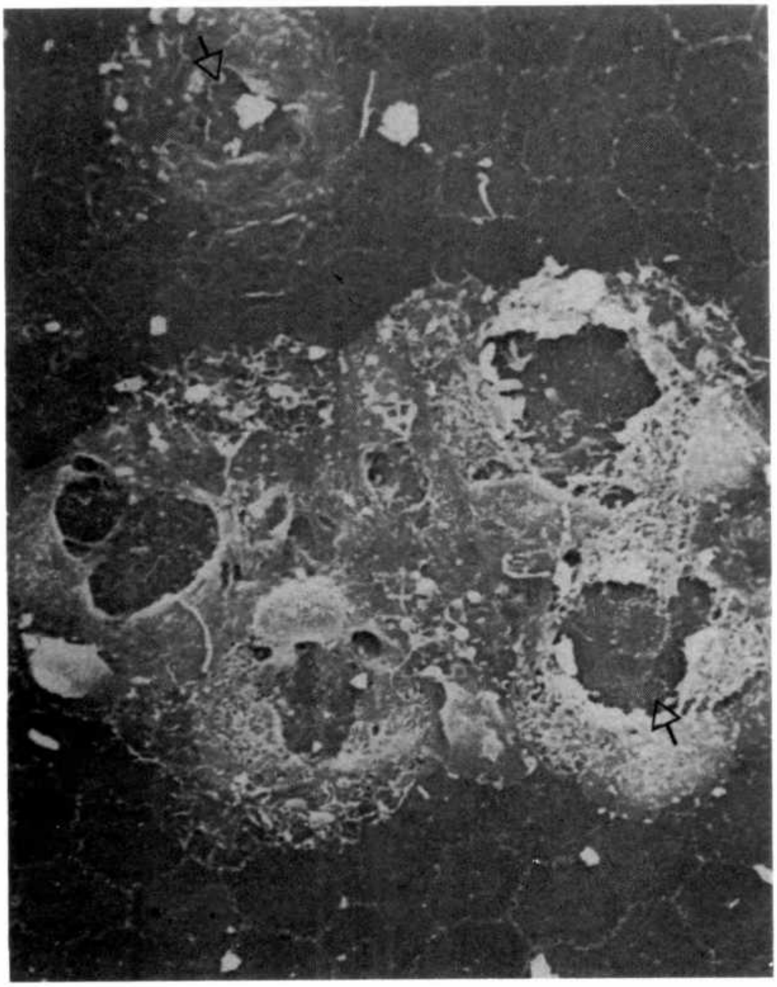

Fig. 3D *Scanning electron micrograph of portion of endothelium in* C. *Arrows identify arrowed lesions in* C. *(×610).*

a bright specular reflex. Fig. 3D is the scanning electron micrograph of the same 'lesion' and shows that the four featureless areas in specular photomicroscopy represent exposed Descemet's membrane, where groups of endothelial cells have been destroyed. The sharp bright image in Fig. 3D of the adjacent tissue represents the inner boundary of a broad band of undercut and raised cells with a finely porous appearance. These correspond to the grey band in the specular image. These cells are undoubtedly irreversibly damaged.[13] The outer limit of the lesion, seen as a dark haze in specular view (Fig. 3C), is well demarcated from adjacent endothelial cells and has either a microvillous or undulating pattern to the posterior endothelial surface (Fig. 3D). This appearance is not associated with permanent cell damage.[13]

Discussion

Both continuous wave (argon or krypton) and short pulsed (Nd/YAG) lasers deliver focused light energy to target tissues. The objective of continuous wave lasers is the deposition of energy within the tissue to induce a temperature rise of sufficient magnitude to coagulate target tissues. This process is dependent upon the degree of tissue pigmentation and density.[14 15] By contrast, the objective of short pulsed lasers is not coagulation but disruption of target tissue by delivering very high power to a very small focus in a highly localised focal plane, which results in the formation of a 'plasma'—a small volume around the focus where irradiated tissues become ionised into a gaseous state (optical breakdown).[16] Target tissues may be transparent, opaque, and/or pigmented. The high powers required for this disruptive facility are achieved in the Q-switched laser by an electro-optical shutter within the laser cavity which permits an accumulation of light energy, so that when the shutter becomes transparent a very short pulse (2–30 ns) of energy can be delivered to the laser focus. It is believed that photodisruption of target tissues is achieved by three interrelated mechanisms.[16] First, focal disintegration of tissue within the plasma due to electron stripping and ionisation; second, shock and acoustic pressure waves created by the tissue recoil around the plasma microexplosion with a maximal effect in tissues adjacent to the plasma; and third, inherent elasticity of the tissues which may enhance the damage created by the first two mechanisms.

Reports of actual and potential unwanted damage to intraocular structures have been directed towards the retina and pigment epithelium with vitreous membrane disruption, to the intraocular lens and retina during capsulotomy, and to the crystalline lens during iridotomy.[5-8 17]

Previous reports of corneal injury describe a clinically insignificant transient haze immediately related to the iridotomies in narrow angled chambers,[1] and endothelial specular microscopical lesions, similar to those in the present paper, after argon laser photocoagulation. The authors attributed the latter changes to the use of a Goldmann contact lens.[18]

In this preliminary study in man, YAG induced corneal endothelial damage occurred in all the iridotomies, and, although concentrated in the immediate vicinity of the laser focus, they were often distributed far beyond. More endothelial damage occurred with multimode operation (focus diameter 70 μm)[5] than the fundamental mode (focus diameter 7 μm)[5] operation.

Specific corneal endothelial damage after laser iridotomy and capsulotomy has not been described previously, yet in this study all iridotomies and all capsulotomies without an intraocular lens implant in situ developed multiple endothelial lesions.

Although the extent and site of the lesions varied following iridotomy and capsulotomy, they appeared similar by specular microscopy.

With the explosive nature of Nd/YAG photodisruption and the post plasma particulate dispersion throughout the anterior chamber borne in mind, the specular microscopical changes suggest a high velocity impact injury to the endothelium with maximal damage in the centre of the lesion and graduated centrifugal changes. The scarcity of lesions following laser capsulotomy in the pseudophakic eye suggests that the implant may act as a barrier against particulate dispersion.

From the specular appearance alone it is not always possible to determine the nature of the endothelial lesion. For example, a temporary alteration in cell structure, such as microvilli of the posterior endothelial surface, may distort the specular image in a similar pattern to that induced by an irreversibly damaged cell.[12]

However, the similarity of the specular microscopical appearances of the induced lesions in the in vitro rabbit endothelium to those in patients indicates that their nature is the same. Because of the facility for precise cell to cell correlation of rabbit specular and scanning electron microscopical appearances it is possible to determine which specular changes represent reversible, and which irreversible, endothelial damage and to a degree to interpret the specular images in man. For example, isolated cells which appear dark and poorly defined in the specular image, that may obscure parts of the adjacent cells or form the peripheral dark collarette of the larger lesions, are found in both rabbits and man. SEM of the former shows these to be due to an excess of microvilli—and this is a reversible change.[12]

By contrast lesions of an irreversible nature, which may involve single or large groups of cells, are well demarcated and often have dark featureless centres surrounded by a variable grey band interspersed with fine brighter reflecting particles. SEM of the rabbit

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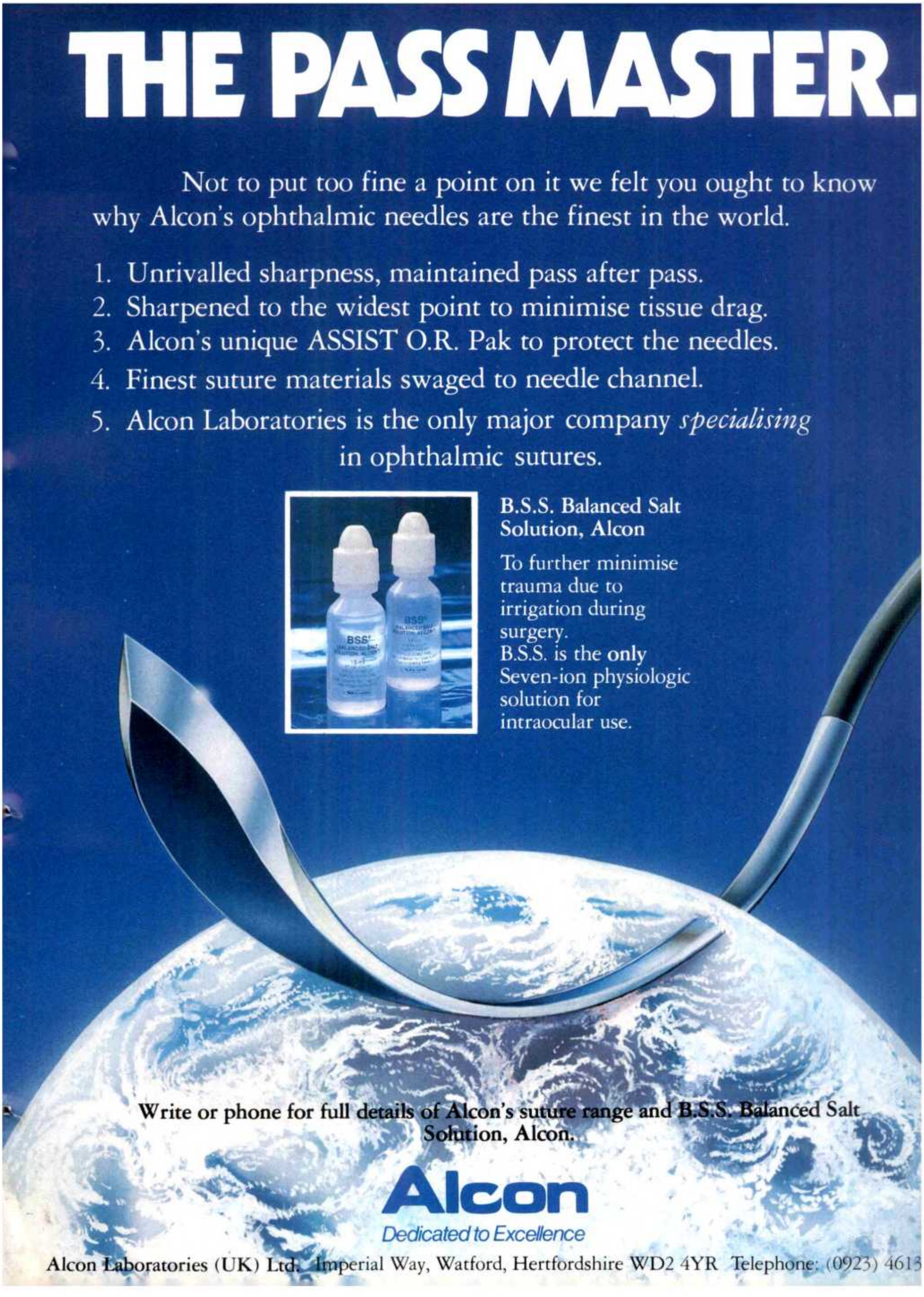

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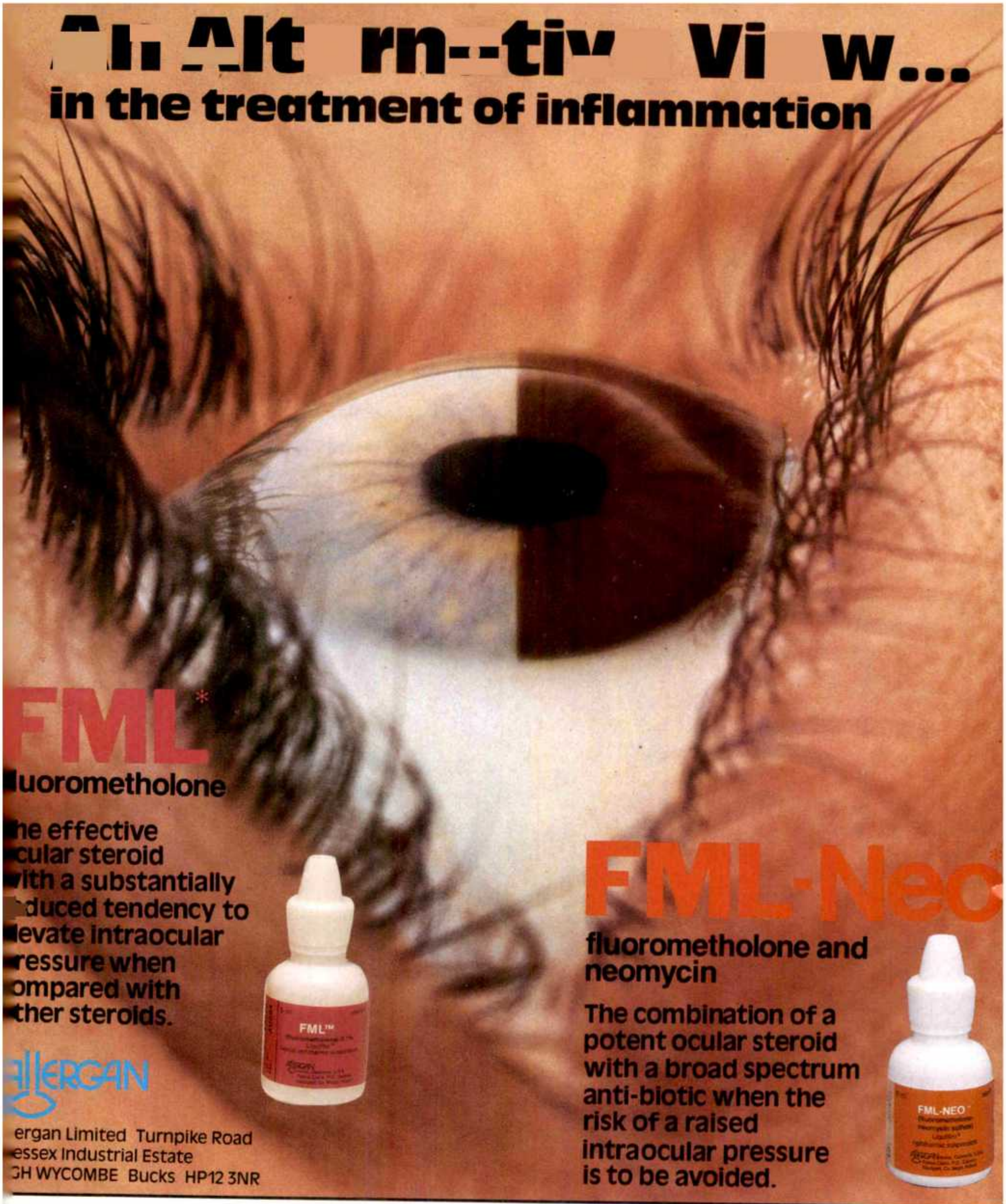

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Presentation Sterile, white, microfine ophthalmic suspension containing fluorometholone, NF 0.1% and neomycin sulphate BP 0.5% (equivalent to 0.35% neomycin base). **Uses** FML-NEO* is indicated for the management of steroid responsive inflammation of the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe, when threatened or complicated by infection with neomycin-sensitive organisms. **Dosage and Administration** One or two drops in the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to discontinu treatment prematurely. Shake well before using. **Contra-indications, Warnings etc.** Acute untreated purulent ocular infections. Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the conjunctiva and cornea. Ocular tuberculosis, fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As for FML* above and, in addition in diseases due to micro-organisms resistant to neomycin, infection may be masked enhanced or activated b the steroid. Prolonged use may result in overgrowth of nonsusceptible organisms. Articles in current medical literature indicate a increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If sensitivi or other untoward reactions occur discontinue the medication. **Precautions** Patients with histories of herpes simplex keratitis should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protracted use of topical steroids during pregnancy has not been substantiated. Local side effects of steroid therapy ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not freeze. **Legal Category** POM. **Package Quantities** Available in 5ml plastic dropper bottles. Basic NHS cost (as at July 1984) £1.90. PL 0426/0043. Prescribing information is available on request.

*Trade Mark

FMN

specimens shows these to be circular areas of exposed Descemet's membrane surrounded by a number of disrupted cells with an outer collarette of cells bearing excess microvilli.

The variation in the absolute numbers of cells lost may be attributable to several factors: the target tissue/endothelium distance, the nature of the tissue being disrupted, differences in delivery of the laser energy (for example the number of bursts, the number of pulses per burst, and the mode of delivery), and the quantity of energy itself. Further studies are necessary to identify the significance of each of these factors.

The majority of eyes that receive YAG laser treatment to the anterior segment have had either previous surgery or a condition which may result in a depletion of endothelial cells.[19] Thus the additional cell loss associated with the YAG laser will be less well tolerated and may, in time, lead to corneal decompensation as a result of normal age related cell loss.[20] Or, as in one of the cases described above, the confluence of lesions led to corneal oedema within one hour of YAG treatment—with a change in the corneal thickness from 0·52 mm to 0·62 mm. At six weeks this cornea remained decompensated with a thickness of 0·58 mm.

CONCLUSION

To quote Saiichi Mishima: 'endothelial damage must be evaluated in its long-term course, and we cannot emphasise too much the importance of minimising trauma to the endothelium during intra-ocular surgery'[21]—and, we would add, laser photodisruption.

We thank the surgeons of Moorfields Eye Hospital for referring their patients for endothelial specular microscopy, Mr Roger Buckley and Professor John Marshall for helpful criticism, Miss C Smyth for typing the manuscript, and Mr W Ng for technical assistance.

References

1 Fankhauser F, Roussel P, Steffen J, Van der Zypen E, Chrenkova A. Clinical studies on the efficiency of high power laser radiation upon some structures of the anterior segment of the eye. *Int Ophthalmol* 1981; **3:** 129–39.

2 Fankhauser F, Lortscher H, Van der Zypen E. Clinical studies on high and low power laser radiation upon some structures of the anterior and posterior segments of eye. *Int Ophthalmol* 1982; **5:** 15–32.

3 Aron-Rosa D, Aron JJ, Grisemann M, Thyzel R. Use of the neodymium YAG laser to open the posterior capsule after lens implant surgery: a preliminary report. *Am Intraocular Implant Soc J* 1980; **6:** 352–4.

4 Aron-Rosa D. Use of a pulsed neodymium YAG laser for anterior capsulotomy before extracapsular cataract extraction. *Am Intraocular Implant Soc J* 1981; **7:** 332–3.

5 Fankhauser H. *Working principles and clinical results with the Q-switched laser.* LASAG AG Instruction manual for Sirius Microruptor II. LASAG AG: 1982.

6 Ready JF. *Effects of high-power laser radiation.* New York: Academic Press, 1971; 213–316.

7 Marshall J. Thermal and mechanical mechanisms in laser damage to the retina. *Invest Ophthalmol Visual Sci* 1970; **9:** 97–115.

8 Jampol LM, Goldberg MF, Jednock N. Retinal damage from a Q-switched YAG laser. *Am J Ophthalmol* 1983; **96:** 326–9.

9 Bonney CH, Gaasterland DE. Low-energy Q-switched ruby laser iridectomies in Macaca mulatta. *Invest Ophthalmol Visual Sci* 1979; **18:** 278–87.

10 Puliafito CA, Steinert RF. Laser surgery of the lens; experimental studies. *Ophthalmology* 1983; **90:** 1007–12.

11 Sherrard ES, Buckley RJ. Contact clinical specular microscopy of the corneal endothelium: optical modifications to the applanating objective cone. *Invest Ophthalmol Visual Sci* 1981; **20:** 816–20.

12 Sherrard ES. Interpretation of specular microscopical images of insulted corneal endothelium by scanning electron microscopy. *Exp Eye Res* in press.

13 Sherrard ES. Intraocular lens damage to the endothelium of *in vitro* rabbit corneae: a specular and scanning electron microscopical study. *Trans Ophthalmol Soc UK* in press.

14 Mainster MA, White TJ, Tips JH, Wilson PW. Retinal temperature increases produced by intense light sources. *J Opt Soc Am* 1970; **60:** 264–7.

15 Mainster MA, White TJ, Allen RG. Spectral dependence of retinal damage produced by intense light sources. *J Opt Soc Am* 1970; **60:** 848–55.

16 Mainster MA, Sliney DH, Belcher CD, Buzney SM. Laser photodisruptors; damage mechanisms, instrument design and safety. *Ophthalmology* 1983; **90:** 973–91.

17 Goldman AI, Ham WT, Mueller HA. Mechanisms of retinal damage from the exposure of rhesus monkeys to ultrashort laser pulses. *Exp Eye Res* 1975; **21:** 457–69.

18 Makitie J, Vannas A, Ahonen R, Teir H. Effects of contact glass and photocoagulation on the corneal endothelium. In: *Acta XXIV International Congress of Ophthalmology.* Philadelphia: Lippincott, 1982; **1:** 267–72.

19 Bigar F, Witmer R. Corneal endothelial changes in primary acute angle-closure glaucoma. *Ophthalmology* 1982; **89:** 596–9.

20 Laing RA. Specular microscopy of the cornea. In: Zadunaisky JA, Davson H. eds. *Current topics in eye research.* New York: Academic Press, 1980; **3:** 157–218.

21 Mishima S. Clinical investigations on the corneal endothelium. *Ophthalmology* 1982; **89:** 525–30.

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In vitro studies with a pulsed neodymium/YAG laser

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SUMMARY The relationships between the destructive effects of Q-switched Nd/YAG laser pulses and a number of experimental parameters were studied for various target materials including in particular excised, fixed samples of human trabecular meshwork. The laser parameters altered were the pulse energy, the convergence angle of the focused beam, and the position of the focus of the beam relative to the target's axial position. The main finding was that it was possible to make deep holes, of a diameter less than 100 μm, in virtually transparent samples of trabecular meshwork with a laser delivery system of 6° convergence and pulse energies of 14 mJ or more. The relevance of this and the other experimental results to the development of a reliable system for performing internal trabeculotomies for the treatment of open-angle glaucoma is presented.

Over the past few years interest has grown in the possible applications of high power pulsed neodymium/YAG lasers in ophthalmology, particularly in the destruction of transparent tissues. Mode-locked Nd/YAG lasers, which give extremely high power and low energy pulses, have been used successfully clinically to open the anterior lens capsule before extracapsular extraction, to pierce secondary membranes, to treat pupillary block and updrawn pupil, and to cut vitreous bands.[1 2] Q-switched neodymium/YAG lasers, which give higher pulse energies but lower peak powers, have been used experimentally on tissues of the anterior chamber,[3] and more recently clinical success had been reported in a range of treatments—iridectomy, membranotomy in pseudophakia, membranotomy and dissection of vitreous bands,[4] coreplasty, and the division of synechiae.[5]

Our long term objective is to develop a system based on a Q-switched Nd/YAG laser to perform internal trabeculotomies as a possible treatment for open-angle glaucoma. Previous attempts by others to use Q-switched pulses to treat open-angle glaucoma have not been successful possibly because of the collapse of Schlemm's canal around the site of the laser hole.[6] Cases where new channels into the suprachoroidal space have been made have also failed to produce a lasting reduction in intraocular pressure.[7] We would hope to avoid the risk of inducing Schlemm's canal to collapse by making laser holes of very small diameter, say 50 μm, spaced around the band, each penetrating the meshwork through to the canal. The demands of such a technique on precision of focusing, reproducibility of the laser output, and confidence in its predicted effect would be great, and, as a first step towards our objective, a series of systematic studies was carried out to investigate the relationships between the observed destructive effects of Q-switched pulses and experimental parameters such as pulse energy, convergence angle of the focused beam, and the nature of the target.

Materials and methods

The laser system used in these studies was the Hyper-YAG 2000 produced by JK Lasers Ltd. It was operated at its fundamental wavelength of 1·06 μm. Pulse durations were compressed to between 30 and 40 ns by Q-switching, so that high powers could be achieved with relatively low energies. A fast photodiode detector (Centronic APD 05 4R) was used to check the pulse duration occasionally. One of its typical output traces, proportional to pulse power versus time, is shown in Fig. 1.

The laser pumping voltage could be altered to vary the pulse energy. The actual pulse energy output was measured before and after each experiment with a photodiode based energy monitor (JK Lasers Ltd). In these experiments the pulse energies used were in

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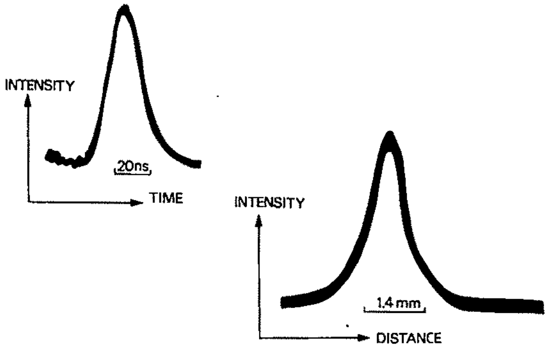

Fig. 1 *Temporal and spatial intensity profiles of Q-switched Nd/YAG pulses.*

the range from 3 mJ to 30 mJ corresponding to pulse powers in the range from 10^5 to 10^6 W.

The laser output was carefully channelled into its fundamental transverse mode, which offered two advantages—the theoretical limit for the focused beam diameter is smaller than for other modes, and the variability in the pattern of intensity from one pulse to another is minimised. The mode pattern of the unfocused Nd/YAG beam was measured periodically with a photodiode array detector (EG and G Reticon RL 512G), and adjustments were made to the laser cavity optics if necessary to regain the fundamental mode. Fig. 1 shows a typical output trace proportional to pulse power versus distance. From such spatial intensity profiles the beam diameter was found to be 1·5 mm. (The diameter is measured across the beam at the points where the signal intensity is 1/e (that is, 1/2·718) of its peak value.)

Fig. 2 shows the experimental arrangement used for these studies. A low power continuous wave helium neon laser beam was directed coaxially into the invisible Nd/YAG beam to mark its path and allow visual focusing. The delivery system supplied with the laser was removed, and the two beams were delivered to the target through a beam expanding telescope and a single focusing lens. Different lenses could be used in this position to converge the Nd/YAG beam at different angles.

The target was mounted on a micropositioning stage, so that its position along the axis of the beams could be altered and set with precision relative to the point at which the HeNe beam could be seen to be focused. The viewing system used to observe this focusing, and so position the target, was quite separate from the laser focusing optics and consisted of a binocular microscope with fibre optic illumination.

Glutaraldehyde-fixed human tissue, obtained at necropsy was used in this study. As the eventual objective was to make holes through the outflow system, many of the experiments used excised pieces of anterior chamber angle tissue with the uveal meshwork surface facing the Nd/YAG beam. In some cases a suspension of saccharated iron oxide was injected into Schlemm's canal in an attempt to mimic the in vivo situation when blood might be present in the canal and, if so, might affect the tissue response to the laser radiation. Corneal tissue was also used as a target, because in the clinical application of this work the converging Nd/YAG beam would pass through the cornea on its way to the meshwork. It was therefore necessary to know whether the cornea would be likely to suffer damage when situated only a few mm away from the focal spot of the Nd/YAG beam.

A smooth, transparent plastic material (Mylar) was also chosen to act as a relatively homogeneous and reproducible non-biological target.

The morphology of the destructive effects of the Nd/YAG laser pulses on the various targets was studied primarily by scanning electron microscopy (Jeol Ltd JSM-T200), for which the tissue samples were prepared by critical point drying. Image analysis (Micro Measurements Ltd, Optomax) was carried out on the scanning electron micrographs to give measurements of hole areas, and a stereoscope with a parallax measurement unit (Cartographic Engineering Ltd) was used on tilted pairs of micrographs to give hole depth measurements. Some of the scanned tissue specimens were reprocessed for Araldite embedding by a technique to be described elsewhere, and 1·0 μm toluidine blue stained sections were

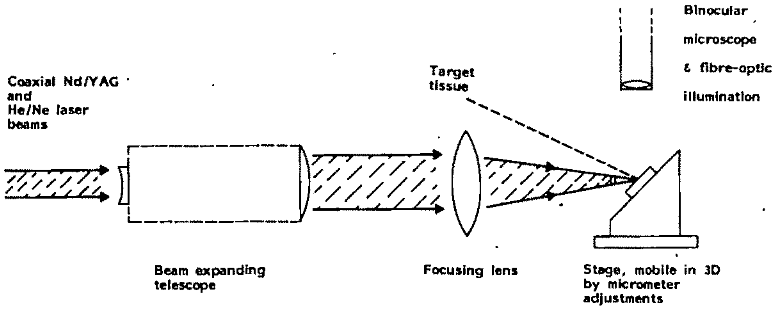
Coaxial Nd/YAG and He/Ne laser beams
Target tissue
Binocular microscope & fibre-optic illumination
Beam expanding telescope
Focusing lens
Stage, mobile in 3D by micrometer adjustments

Fig. 2 *Schematic diagram of experimental delivery system.*

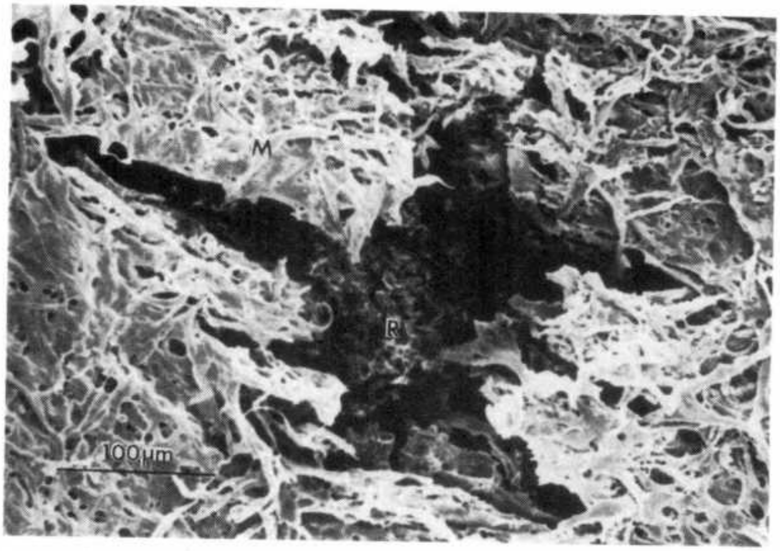

Fig. 3 *Laser hole made by a single 30 mJ pulse converging at 2° on to tissue positioned at the HeNe focus. M = Uveal meshwork; R = Red blood cells.*

studied by light microscopy (Leitz Dialux 20/Wild Photoautomat MPS 45).

Procedure and results

Six sequential sets of experiments were carried out as follows:

Meshwork tissue at low convergence angle. A lens of focal length 52 mm was used to focus the Nd/YAG beam on to the uveal surface of meshwork samples. This would give a beam convergence angle of only 2°, much lower than we expected to use in our in vivo application, but it did offer a long working distance, which was very useful in this preliminary work. Single pulses of 30 mJ each were fired into tissue positioned at the point of focus of the HeNe beam. Determining this focal point with a precision of even 100 μm was found to be difficult.

Scanning electron microscopy of the tissue samples subsequently showed well defined holes at 13 out of 22 target sites. Holes that were clearly seen to penetrate through to Schlemm's canal were made in five cases. Fig. 3 shows one of these holes.

Measurements of hole area and depth yielded coefficients of variation of over 70% indicating great variability in the dimensions of holes made in trabecular tissue under apparently identical conditions. In nine cases no hole was made at all. A simpler target material was therefore chosen for the next set of experiments.

Mylar at low convergence angle. Single pulses of 10 mJ were fired into plastic placed at a series of positions between 0·5 mm in front of the HeNe focus and 3·5 mm beyond it. The plastic was then coated with gold and observed by scanning electron microscopy.

Large variations were again found in hole area and depth at a given target position shown by coefficients of variation of approximately 50%. Possibly because

```
MYLAR    at                11.0 mJ      -   ±         +          + + +      + +   ±    + + ±   -
MYLAR    at                 6.0 mJ          -   -   ±   +   +    +   +   +    -   -


CORNEAL ENDOTHELIUM    at  30.0 mJ                         - -++ + + + + -
CORNEAL ENDOTHELIUM    at  13.0 mJ                           - + + + + + -
CORNEAL EPITHELIUM     at  11.0 mJ                           - + +   + - -

                                         -1.0                    0                  +1.0
                                         TARGET DISPLACEMENT FROM HeNe FOCUS (mm)
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Fig. 4 *Effects of Nd/YAG pulses at a convergence angle of 6° targeted on Mylar and human cornea. + = Hole made; − = No hole made.*

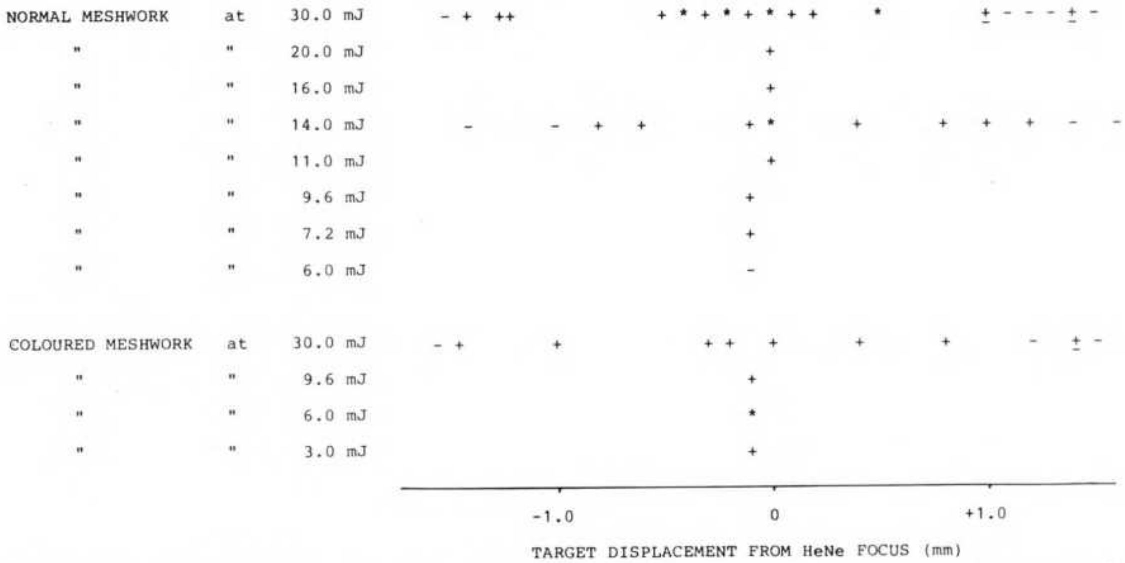


Fig. 5 *Effects of Nd/YAG pulses at a convergence angle of 6° targeted on normal and artificially coloured human meshwork. + = Hole made; * = Hole extending through to Schlemm's canal made; – = No hole made.*

of this no systematic change in area or depth with target position was observed. The main finding was that all 75 target sites fired at did show laser damage, though the target position had varied over a range of 4 mm. The effective depth of focus of this delivery system was at least 4 mm then, obviously too large for the intended clinical application. The focusing lens was therefore replaced with one of shorter focal length for the next set of experiments.

Mylar at high convergence angle. A lens of focal length 14·6 mm was used to focus Nd/YAG pulses at a convergence angle of 6° on to pieces of Mylar held at a series of positions between 1·2 mm in front of the HeNe focus and 1·4 mm beyond it. Single pulses of either 6 mJ or 11 mJ were used.

The results are indicated in the upper section of Fig. 4. They show that 11 mJ made holes over a target position range of approximately 2 mm, so the depth of focus of the delivery system had indeed been reduced. It can also be seen that the depth of focus was reduced from 2 mm to approximately 1 mm by lowering the pulse energy to 6 mJ. While carrying out

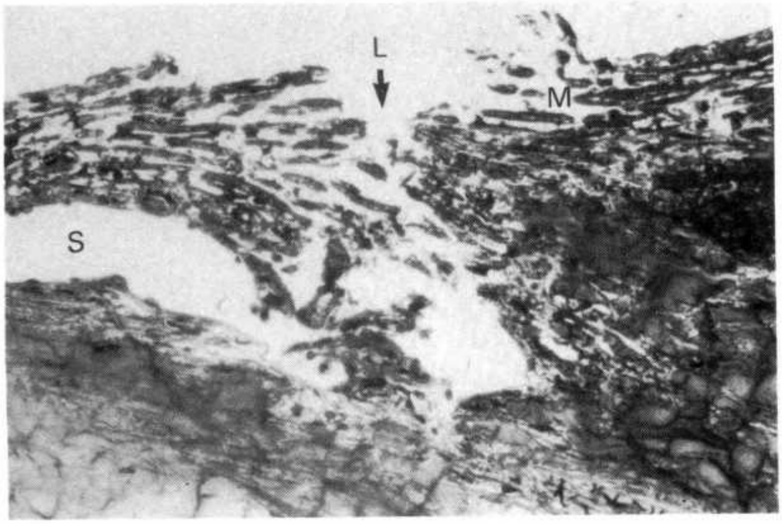


Fig. 6 *A toluidine blue stained 1μm section of tissue previously positioned 0·5 mm beyond the HeNe focus and exposed to a single 30 mJ pulse at 6° convergence. S = Schlemm's canal; L = Laser hole; M = Uveal meshwork. (×298).*

this set of pulse firings we found it possible to locate the HeNe focus with a precision of approximately 10 μm with this high convergence system. These results were encouraging enough to warrant tissue experiments with the same system.

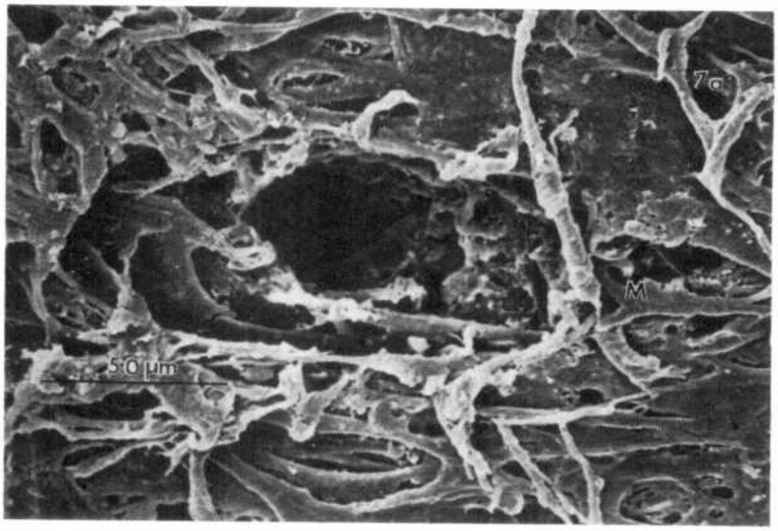
Cornea at high convergence angle. Nd/YAG pulses, converged at an angle of 6°, were fired into corneal tissue held at positions between 300 μm in front of the HeNe focus and 400 μm beyond it. Single pulses of 30 mJ, 13 mJ, or 11 mJ were fired into each target site. In some cases the corneal tissue was positioned with its epithelial surface facing the Nd/YAG beam. In others the endothelial surface was exposed instead.

The results are indicated in the lower section of Fig. 4. It was found that even at 30 mJ, Nd/YAG pulses caused damage only if the corneal surface was positioned between 100 μm in front of the HeNe focus and approximately 300 μm beyond it. Such a small depth of focus for damage in the cornea suggested that the 6° convergence angle system would be acceptable in that context for our eventual in vivo application.

Normal meshwork at high convergence angle. Excised samples of meshwork were held at a series of positions between 1·5 mm in front of the HeNe focus and 1·6 mm beyond it. Eight different Nd/YAG pulse energies in the range 6 mJ to 30 mJ were tried, firing a single pulse into each target site as before.

The results are indicated in the upper section of Fig. 5. There were four main points of interest in

Figs. 7A and B *Scanning electron micrographs of tissue exposed to Nd/YAG pulses at 6° convergence.*



A: *Effect of one 30 mJ pulse fired into tissue position at 0·2 mm beyond the HeNe focus. M=Uveal meshwork.*

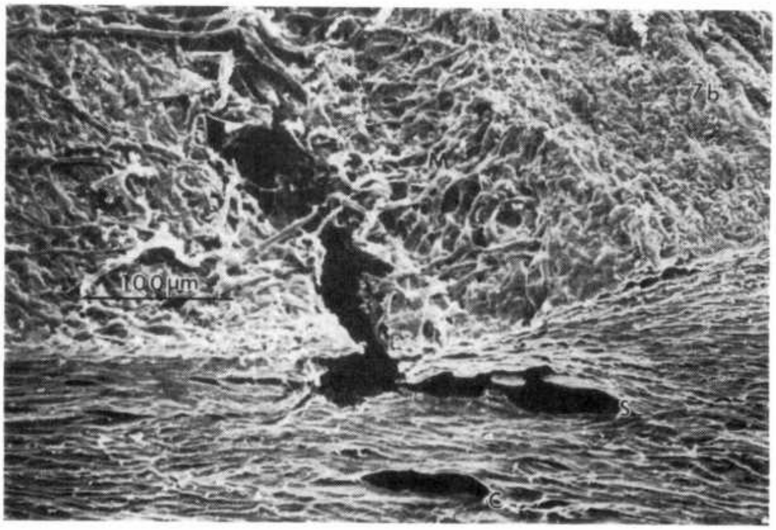


Fig. 7B: *Effects of two 14 mJ pulses fired side by side into tissue positioned first at the HeNe focus then 0·4 mm beyond it. M=Uveal meshwork; S=Schlemm's canal; C=Collector channel.*

them. The effective depth of focus for making holes in meshwork with 30 mJ pulses was approximately 2·4 mm centred at the point of focus for the HeNe beam. This depth of focus was reduced as pulse energy was lowered. The threshold for meshwork damage was about 7 mJ. The deeper holes were made when the target was closer to the HeNe focal point.

It was found that holes as small as 50 µm in diameter but extending into Schlemm's canal could be made. Fig. 6 is a photomicrograph of a toluidine blue stained section cut through one of the laser holes. Fig. 7 shows scanning electron micrographs of some others.

Stained meshwork at high convergence angle. Four values of pulse energy in the range 3 mJ to 30 mJ were tried with the artificially coloured meshwork samples. In other respects the experimental protocol was as for the previous set of experiments.

The results are shown in the lower section of Fig. 5. It was found that 30 mJ pulses made holes over approximately the same range as for unstained tissue, but the threshold of damage was much lower. Even the lowest Q-switched pulse energy available with our system, 3 mJ, resulted in a hole, and one pulse of only 6 mJ made a hole through to Schlemm's canal.

These results can be explained as follows. Laser damage by Q-switched pulses can occur by non-linear processes of fundamental structural breakdown,[8] but only at very high power densities, of the order of 10^{10} watt/cm^2. These processes would be expected to apply to transparent and coloured matter equally, and our results at a pulse energy of 30 mJ confirm this. At lower power densities damage can occur by normal, linear absorption processes. The effectiveness of these processes would be expected to depend on the properties of the target matter, in particular its colour. Our results below 7 mJ fit this reasoning.

Discussion

This series of in vitro experiments has yielded information of interest and value in furthering our development of a noedymium/YAG laser system for performing internal trabeculotomies. The initial work, done with a small YAG convergence angle, showed the feasibility of making discrete holes through meshwork but also showed problems of poor reproducibility of the effects in terms of the dimensions of the holes made. This variability was found to depend partly on the irregularity of the tissue surface, as it improved slightly if a smooth plastic surface was used instead, but also on the difficulty found in accurately determining the focal point of the HeNe marker beam.

When the convergence angle of the two laser beams was increased by a factor of three, the focal point of the HeNe beam could be found more reliably, and at the same time the effective depth of focus for the YAG pulses was significantly reduced resulting in a more useful delivery system.

This system enabled the effects of displacing the target from the geometric focus, of lowering pulse energy, and of changing the nature of the target to be observed. Although these effects could have been predicted qualitatively, our system allowed precise measurements of the changes and corresponding effects to be made. It also showed that holes of the required morphology—diameter 100 µm and depth sufficient to reach Schlemm's canal—could be created quite easily.

Similar in vitro studies are currently being pursued with fresh tissue rather than fixed being used, an even larger beam convergence angle, and a specially designed gonioglass, to approach the in vivo situation more closely. In this way we hope to gather systematically the data on which a clinical neodymium/YAG laser system and operating protocol can be soundly based.

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References

1 Aron-Rosa D, Griesemann JC, Aron JJ. Applications ophtalmologiques des lasers neodymium YAG pulses—Ouvertures preoperatoires des cristallins avant implants et des cataractes secondaire derrière implants cristalliniens. *J Fr Ophtalmol* 1981; **4:** 61–6.

2 Aron-Rosa D, Cohn HC, Aron T. Use of a pulsed neodymium-YAG laser (picosecond) in endocular surgery. In: Birngruber R, Gabel V-P, eds. *Laser treatment and photocoagulation of the eye.* Amsterdam: Junk, 1984.

3 Van der Zypen E, Bebie H, Fankhauser F. Morphological studies about the efficiency of laser beams upon the structures of the angle of the anterior chamber. *Int Ophthalmol* 1979; **1:** 109–22.

4 Fankhauser F, Lortscher H, Van der Zypen E. Clinical studies on high and lower power laser radiation upon some structures of the anterior and posterior segments of the eye. *Int Ophthalmol* 1982; **5:** 15–32.

5 Fankhauser F, Roussel P, Steffen J, *et al.* Clinical studies upon some structures of the anterior segment of the eye. *Int Ophthalmol* 1981; **3:** 129–39.

6 Van der Zypen E, Fankhauser F. The ultrastructural features of laser trabeculopuncture and cyclodialysis. *Ophthalmologica* 1979; **179:** 189–200.

7 Van der Zypen E, Fankhauser F. Lasers in the treatment of chronic simple glaucoma. *Trans Ophthalmol Soc UK* 1982; **102:** 147–53.

8 Bloembergen N. Laser-induced electric breakdown in solids. *IEEE J Quant Electr* 1974; **QE10:** 375–86.

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Thermal lens measurements in the cornea

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SUMMARY Q-switched pulses from a neodymium/YAG (yttrium-aluminium-garnet) laser were passed through corneal discs taken from the enucleated eyes of three baboons and four rabbits. The time course of heat dissipation following absorption of laser energy by the tissue was studied with the use of a second continuous wave laser beam acting as a probe. It was found that the absorption of each neodymium/YAG pulse created a transient divergent lens within the cornea as theoretical considerations predicted. The relaxation time that characterised the decay of this thermal lens for a 1/e laser beam diameter of 2·0 mm was found to be 2·3±0·1 s (mean ± standard error for 12 separate groups of measurements). Our results show that Q-switched laser pulses passing through apparently unaffected transparent tissues can induce thermal lens effects which persist for several seconds. The optical transfer of each pulse in a stream will be identical only if enough time is left between pulses for the tissues to return to their initial state. Therefore, when such laser pulses sharply focused to perform high precision intraocular surgery are used, thermal lensing in the transparent ocular media must limit the rate at which pulses can be usefully delivered.

Thermal lens effects were first discovered in 1964 by Gordon *et al.* in the course of studies on Raman scattering in liquids. They subsequently developed a model that could quantitatively explain their observations.[1] Our current understanding of the phenomenon may be simply summarised as follows.

Thermal lensing is the creation of variations in refractive index within a virtually transparent medium following the passage of a laser beam through it. It occurs because absorption of energy from a laser beam passing through a substance, which may be solid, liquid, or gas, raises the temperature locally in a pattern that matches the intensity profile across the width of the laser beam. This quickly leads to corresponding density changes and thus to changes in refractive index. For many materials the refractive index is lowered with temperature, and this reduction must be greatest at the centre of the laser beam where the light intensity is highest. In effect a diverging lens is formed within and by the absorbing substance. The focal length of the lens depends on the nature of the substance and on the laser pulse's power. With time, if no further laser radiation is passed through, all the absorbed energy is thermally dissipated into the bulk of the substance, and the thermal lens effect is lost. The rate of loss depends on the thermal properties of the substance and the diameter of the laser beam. Fig. 1 illustrates the formation of a thermal lens.

To date thermal lensing has been studied only in gases, liquids, and relatively simple non-biological solids. Now, however, thermal lens effects are of interest in relation to high precision eye surgery by lasers. Recently there has been a lot of interest in the use of short duration, high power laser pulses directed into the chamber angle in the treatment of open-angle glaucoma[2] and in the disruption of vitreal bands, opacified lens capsules, etc.[3] Any such application requires precise focusing, and, although the fraction of laser energy that would be absorbed by the cornea is likely to be small, significant thermal lensing has been found to occur within substances whose absorption coefficients are lower than $10^{-3}cm^{-1}$.[4] It was, therefore, theoretically possible that a laser pulse passing through corneal tissue would create a thermal lens, which would have the effect of defocusing subsequent laser pulses. This investigation was designed to discover whether such lensing really did occur, and, if it did, to follow the time course of its decay.

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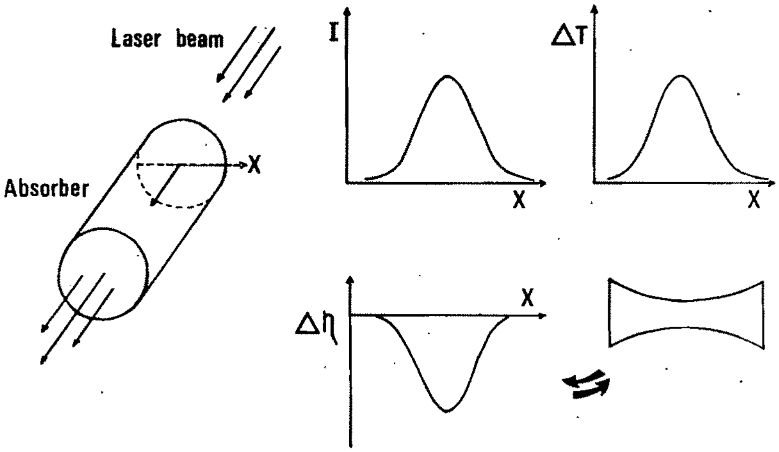

Fig. 1 *The formation of a thermal lens. I = Intensity, ΔT = Temperature change, Δη = Refractive index change, X = Distance across width of laser beam.*

Materials and methods

Unfixed eyes were enucleated immediately after death from four rabbits and three baboons, animals which had been used in other quite separate experiments undertaken by coworkers. The corneal tissue from these animals is physically very similar to that of humans. The eyes were then immersed in chilled Barany's solution and transported to the laser laboratory within 30 minutes. Discs of corneal and limbal tissue were excised from these eyes. The scleral rim of each corneal disc was attached to a metal ring with Histoacryl Blue tissue adhesive and placed within a transparent cell filled with Barany's solution (Fig. 2). The experimental apparatus was arranged so that the parallel output beam of a pulsed neodymium/YAG laser (JK Lasers Ltd, Hyper-YAG 2000 system) would pass through the central thickness of the cornea and then be diverted into an absorbing block. To test for thermal lensing a second laser beam, from a low power continuous wave helium neon laser, was passed coaxially through the cornea. This tracer beam was then directed through a pinhole aperture and a narrow band pass filter on to a photomultiplier tube connected to a transient recorder (Biomation Corp., Biomation 1010) and microcomputer (Apple Computer Inc., Apple II).

With this arrangement if a thermal lens was formed in the cornea by a YAG pulse it would diverge the initially parallel, Gaussian profiled HeNe beam and reduce the intensity detected at the pinhole aperture of the photomultiplier. Initially the pinhole was positioned on the axis of the helium neon beam, where the steady intensity detected was a maximum. The possibility that an apparent thermal lens signal was in fact due to a lateral shift of the HeNe beam was excluded in the following way. As soon as such a signal was detected for the first time the pinhole aperture was moved to each of a set of slightly off axis positions in turn and a YAG pulse fired each time. It

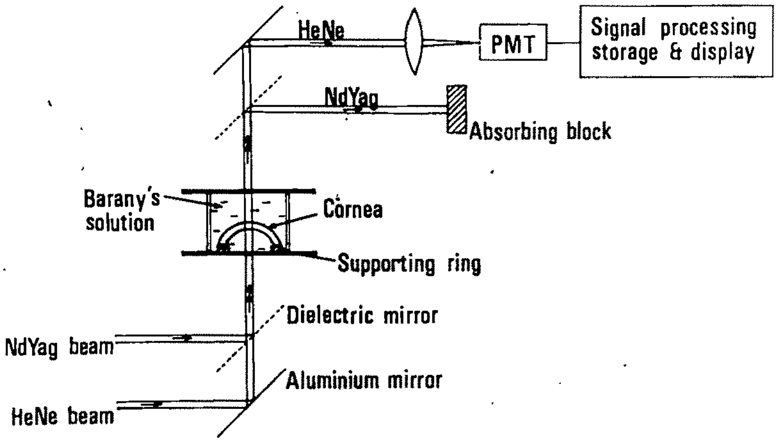

Fig. 2 *Schematic diagram of experimental apparatus.*

was ascertained that the PMT signal was indeed smaller at each position around the original axial one. The first signal must, therefore, have been a true lensing signal signifying divergence of the beam rather than any lateral shift.

The YAG laser was set up to lase in its fundamental transverse mode, confirmed by direct measurements with a photodiode array (EG and G Reticon, RL 512G), and at its fundamental wavelength of 1·06 µm. Pulses were of energy 18 to 22 mJ and duration 25 to 30 ns, giving power densities at the cornea of approximately 10^5 to 10^6 Watt/mm^2 for a 1/e beam diameter of 2·0 mm.

It was ascertained by trial and error that a 10 s gap between the YAG pulses was long enough for the effect of a single YAG pulse to be observed independently of the effect of any other, that is, 10 s was long enough for recovery of the tissue from thermal lensing effects—vi. A stream of these pulses was thus fired at 10 s intervals (over a period of 15 to 20 minutes), and the signal from the photomultiplier was recorded after each pulse. As each individual signal was very small the signal to noise ratio of the measurement was improved by averaging automatically all the signals collected through this time. However, the final signal still represented the effect of a single, if 'typical', YAG pulse.

At least one set of 100 or so results was obtained from each cornea tested. In five instances a second set was obtained by slightly repositioning the cornea to use an adjacent area. Before trying any corneal measurements trial runs were carried out in the sample cell with water, chloroform, and Barany's solution in turn. The first two liquids were chosen as their thermal characteristics have been well established in the past. Barany's solution was tested, as it would be present during the corneal measurements.

Results

Fig. 3 shows a single, typical thermal lens signal after a single YAG pulse was passed through the test cell.

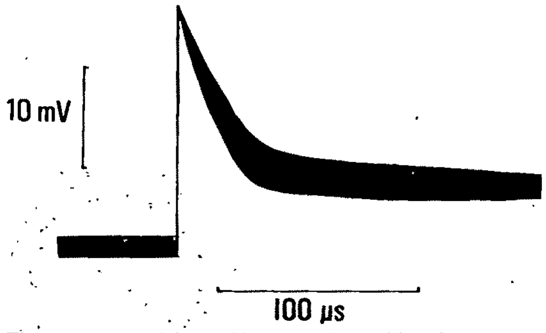

Fig. 3 *A typical thermal lens trace from chloroform.*

This particular trace, the inverse of the HeNe intensity versus time, was recorded from chloroform, but the same general pattern of a very sharp rise and a slow decline was found with the other liquids tried and with the corneae.

Our main interest in this study was the time dependent decay of the thermal lens signals. The signals were sampled, recorded, and analysed by the microcomputer. It used a program based on a model developed and tested by Bailey *et al.* in 1980 and 1981.[5,6] They showed that the time dependence during the period of recovery, when heat conduction acts to dissipate the lensing effect, is determined by a relation time parameter. This parameter τ is characteristic of the absorbing substance concerned and varies with the square of the laser beam diameter. Their full mathematical analysis showed that the thermal lens signal S of the tracer beam is related to τ by the following equation:

$$1/\sqrt{S} \approx t/\tau c + 1/c \ \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ {}^{1}$$

where t is time and c is independent of time and the laser parameters. So if $t=5\tau$ say, $S_{5\tau} \approx c^2/36$ c.f. at $t=0$, $S_0 \approx c^2$

So, after a time of 5τ, the thermal lens signal would drop to about 3% of its peak value.

A plot of the left hand side of equation 1 against time t should, therefore, give a straight line whose intercept divided by slope will yield the value of τ.

In applying this analysis to our study of lensing in corneal tissue this plot and calculation were carried out automatically for each signal within each set of 100 or so measurements. Some runs were carried out

Table 1. *Values of relaxation time τ obtained for corneae and some liquids*

Sample	*Beam diameter (mm)*	*Measured τ (s)*	*τ Corrected to beam diameter of 2·0 mm*
Water	0·9	0·359	1·77
Water	1·5	1·00	1·77
Water	2·0	1·80	1·80
Barany's solution	0·9	0·369	1·82
Chloroform	0·9	0·616	3·04
Cornea			
Baboon 1	1·5	1·1	1·9
Baboon 1	1·5	1·6	2·8
Rabbit 1	1·5	1·4	2·5
Rabbit 1	1·5	1·7	3·0
Baboon 2	1·5	1·2	2·1
Baboon 3	2·0	1·9	1·9
Baboon 3	2·0	1·7	1·7
Rabbit 2	2·0	2·6	2·6
Rabbit 3	2·0	2·8	2·8
Rabbit 3	2·0	2·7	2·7
Rabbit 4	2·0	2·0	2·0
Rabbit 4	2·0	1·5	1·5

at a YAG beam diameter of 1·6 mm and others at 2·00 mm, but as the dependence of τ on beam diameter was known the values of τ were all corrected to a common beam diameter of 2·0 mm. These corrected values of τ are given in Table 1.

For water and Barany's solution values of τ varying from 1·77 s to 1·80 s were obtained. For corneae values lay between 1·5 s and 2·8 s with a mean of 2·3 s ± 0·1 s (standard error of the mean for 12 sets of measurements). For chloroform a value of 3·04 s was obtained.

Discussion

Thermal lensing has been shown to occur with the 1·06 μm beam of a neodymium/YAG laser in water, Barany's solution, and chloroform, and values of the relaxation time parameter τ obtained in each case. When corneal tissue immersed in Barany's solution was tested signals were obtained which persisted for a time significantly longer than that from the solution alone and so must have resulted from lensing in the tissue itself. The experiments have, therefore, shown that corneae do exhibit thermal lensing, and that recovery from lensing due to a laser beam diameter of 2·0 mm is characterised by a relaxation time of 2·3 s.

The values of wavelength, pulse energy, and power density at the cornea chosen for this study are typical of those obtained with Q-switched neomymium/YAG lasers now used in experimental and clinical eye surgery.* One application of such a laser which is of particular interest to us is laser trabeculotomy as a possible treatment of open-angle glaucoma. This is one example of the use of sharply focused Q-switched pulses in ocular surgery which could be adversely affected by the relatively long decay of thermal lensing in corneal tissue. For example, if our laser system were set up to fire one pulse per second the thermal lens created in the cornea by the first pulse will not have had time to decay before the second pulse reaches it. The second pulse will then be focused at a point slightly beyond that of the first pulse. The shift of focus will increase for the third pulse and so on. Only if a time of say 5τ or more is left between one pulse and the next will the defocusing effect be lost.

In fact, reducing the laser beam diameter at the cornea from the 2·0 mm we chose for our experiments would reduce the relaxation time and so allow pulses to be fired at at a higher rate without defocusing, but in practice a diameter of at least this size is necessary to avoid damaging the cornea at the same time as the target tissue.

The magnitude of the defocusing due to thermal lensing in the cornea cannot be predicted from the results of these particular experiments, but there is some outside evidence that it may be of practical significance. Fankhauser *et al.* stated in a recent paper on laser surgery[7] that the focus of their YAG laser, pulsed at a frequency of 50 Hz, shifted by up to 3 mm according to the number of pulses fired in one burst, and that an empirical correction had to be applied when aiming. The authors gave no explanation of this defocusing effect, but the results of our experiments, and in particular the large measured values of corneal relaxation time, suggest that such defocusing could well be due, at least in part, to thermal lensing within the cornea.

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References

1 Gordon JP, Leite RCC, Moore RS, Whinnery JR. Long-transient effects in lasers with inserted liquid samples. *J Appl Physiol* 1965; **36:** 3.

2 Van der Zypen E, Fankhauser F. Lasers in the treatment of chronic simple glaucoma. *Trans Ophthalmol Soc UK* 1982; **102:** 147.

3 Aron-Rosa D, Griesemann JC, Aron JJ. Applications ophtalmologiques des lasers neodymium YAG pulses. *J Fr Ophtalmol* 1981; **4:** 61.

4 Solimini D. Loss measurements of organic materials at 6328 Å. *J Appl Physiol* 1966; **37:** 3314.

5 Bailey RT, Cruickshank FR, Pugh D, Johnstone W. Pulsed source thermal lens Part 1—theoretical analysis. *J Chem Soc (Faraday 2)* 1980; **76:** 633.

6 Bailey RT, Cruickshank FR, Pugh D, Johnstone W. Pulsed source thermal lens. Part 2: Experimental tests of the theory. *J Chem Soc (Faraday 2)* 1981; **77:** 1387.

7 Fankhauser F, Roussel P, Steffen J, Van der Zypen E, Chrenkova A. Clinical studies on the efficiency of high power laser radiation upon some structures of the anterior segment of the eye. *Int Ophthalmol* 1981; **3:** 129.

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*Consider the Sirius-Microruptor 2 system, for example, one of the first and best known Q-switched Nd/YAG laser systems produced commercially for ophthalmic applications. Data supplied by the manufacturer, LASAG AG of Switzerland, show an expected beam area at the cornea of 6 mm^2, which for pulses of up to 70 mJ delivered in 12 ns means corneal power densities of up to 10^6 watt/mm^2. Compare the laser system used in this study which gave, typically, 20 mJ delivered in 35 ns over a corneal area of 3 mm^2, corresponding to a corneal power density of $2 \cdot 10^5$ watt/mm^2.

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Giant retinal tears after central vitrectomy

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SUMMARY Giant retinal breaks developed in four eyes within two months of pars plana vitrectomy. The pathogenesis and implications of this serious complication are discussed.

Closed vitreous microsurgery may be a hazardous procedure, particularly when it is employed in the management of complicated vitreoretinal pathology. The purpose of this report is to highlight the danger of giant retinal tear formation associated with detachment of residual vitreous cortex in eyes that have previously undergone a 'central' vitrectomy via the pars plana.

Case reports

CASE 1

A 27-year-old patient was referred for anterior segment revision in 1978 nine years after a perforating injury that involved the cornea and lens of his amblyopic left eye. Using the Peyman Vitrophage we removed cortico-capsular remnants via a single incision in the superotemporal pars plana. A 'central' vitrectomy was also done, but, since the vitreous was not detached, the postbasal cortical gel remained in situ. No untoward retinal changes, whether preexisting or surgically induced, were identified by indirect ophthalmoscopy. Vision improved to 6/60 with an aphakic correction.

Seven weeks postoperatively flashes and floaters in the left eye were followed by profound visual loss, and examination showed complete separation of the mobile cortical gel remnant up to the posterior border of the vitreous base together with a 180° superior giant retinal tear (9.30 o'clock clockwise to 3.30 o'clock). The residual gel was attached to the anterior margin of the tear, which comprised 1·5 mm of peripheral retina and posterior non-pigmented pars plana epithelium. The posterior flap of the tear was inverted over the disc and macula. The patient declined further surgery.

CASE 2

A 24-year-old Malaysian was referred in 1981 for management of a retinal detachment in his myopic right eye (−8·50 D). He was totally blind in his left eye, which had undergone unsuccessful surgery for a retinal detachment two years previously. B-scan ultrasound on the left eye showed a dense cataract and a funnel shaped retinal detachment (triangle sign) but no features that suggested a giant retinal tear. Vision in the right eye was reduced to 6/36 by an inferotemporal retinal detachment just involving the macula. This was identified as being secondary to an unusual posterior retinoschisis, with multiple tiny inner leaf breaks overlying a large outer leaf break raised from the pigment epithelium immediately inferotemporal to the macula. The right eye underwent a central vitrectomy via three pars plana incisions, for which we used the Kloti 20 gauge vitreous stripper. Since it proved impossible at surgery to remove the vitreous cortex from the region of the inner leaf breaks, only partial internal drainage of schitic and subretinal fluid was achieved through the posterior breaks, but it was possible to apply xenon endophotocoagulation burns around the breaks. A fluid/20% SF6 gas exchange was done together with limited cryotherapy posterior to the pars plana entry sites. Despite appropriate postoperative posturing the breaks reopened once the gas bubble had absorbed. Ten days after the initial surgery, therefore, a further internal drainage was done (again limited by persistent gel attachment around the inner leaf breaks), together with a fluid/silicone oil exchange when three further pars plana incisions were made. Over the next three weeks the retina slowly reattached, and laser photocoagulation was applied through the silicone oil around the outer leaf break to reinforce the previous xenon treatment (acuity 6/18 unaided). The silicone oil was removed three months later by re-exchange for infusion fluid

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via two further pars plana incisions. Postoperatively vision was 6/24 with a myopic correction, and the retina was secure.

Two months after the oil removal floaters appeared in the right vision followed the next day by profound visual loss (acuity, hand motion). Examination showed a superotemporal retinal detachment including the macula (but limited in extent by the posterior photocoagulation) secondary to a 100° giant retinal break at the ora serrata (9.30 o'clock clockwise to 1.00 o'clock). The posterior flap of the tear was partially inverted, it being held in one area by a postoral cryo scar. Residual mobile vitreous cortex was completely detached from the retina (including that posterior portion that had previously blocked the inner leaf holes in the schisis) and was suspended from the anterior oral margin of the giant tear. A further closed microsurgical procedure was therefore done via three more pars plana sclerotomies (numbers 9, 10, and 11). The detached vitreous cortex was removed, and the posterior flap of retina was manipulated into place during a second fluid/silicone oil exchange. Cryopexy was applied to the repositioned edge of the posterior flap and through 360°. The retina remained attached (acuity 6/24 unaided), but the eye developed a raised intraocular pressure associated with silicone emulsion in the chamber angle. Further laser applications were applied to the posterior edge of the giant break, and five weeks after the second silicone exchange the silicone oil was removed and a trabeculectomy was done. Eighteen months later right vision was 6/24 with a myopic correction. The intraocular pressure was within normal limits. There was mild cataract, and the retina was entirely attached.

CASE 3

A 23-year-old student with Marfan's syndrome was referred for vitreolensectomy in 1984. He had bilateral superonasal lens subluxations. The inferotemporal equators of the clear lenses crossed the visual axes and interfered with near vision (acuity 6/18, N6 RE; 6/36, N18 LE). A left vitreolensectomy was done. We used the Ocutome and three pars plana incisions (superonasal, superotemporal, and inferotemporal); the cortical gel was left in situ attached to the postbasal retina. Prophylactic monitored 360° confluent cryotherapy was applied immediately posterior to the retroplaced ora serrata. No oral or peripheral retinal abnormality was detected at surgery or initially thereafter. Vision improved to 6/4; N5 with the help of a contact lens.

Two months after surgery floaters became apparent in the left eye, though acuity was unaffected. Examination showed a completely detached mobile vitreous cortex and a 190° giant retinal tear at the ora serrata (12 o'clock clockwise to 6.30 o'clock) with a raised anterior flap comprising non-pigmented pars plana epithelium from which the gel remnant was suspended. The retina posterior to the tear was entirely attached and secured by the previous cryo scars. No treatment was thought to be necessary, and central vision was maintained at 6/4 six months after giant tear formation with no evidence of epimacular proliferation.

Because of the excellent acuity obtained in his left eye, the patient requested similar surgery for his right eye. Prophylactic 360° postoral cryopexy was performed six weeks prior to right vitreolensectomy via the pars plana. The vitreous cortex was noted to be attached at operation, and since it could not be readily separated from the retina the vitreous 'rim' was left in situ. One month later the patient noticed floaters in his right eye, and examination revealed pigment-cell invasion of the detached vitreous cortex and a virtually 360° giant retinal tear at the ora serrata. As in the left eye, the retina remained attached and vision was maintained at 6/4.

Discussion

The mechanism of formation of giant retinal tears (GRTs) is controversial. While the role of posterior vitreous detachment (PVD) has been questioned in the past,[1] experience during vitrectomy suggests that PVD (and consequent dynamic vitreoretinal traction[2]) is the predominant pathogenic mechanism except after blunt trauma[3] (often associated with extensive vitreous base avulsion—'bucket-handle tears'). GRTs also complicate PVD after posterior penetrating trauma with vitreous incarceration. These two elements—basal gel incarceration (an inevitable complication of pars plana entry wounds) and dynamic vitreoretinal traction (after detachment of retained vitreous cortex posterior to the vitreous base)—appear to have combined to produce the GRTs in these three cases (Fig. 1).

GRTs can occur at the time of vitrectomy[4] either in the region of an 'active' pars plana entry site (especially during multiple instrument insertions and removals), or elsewhere (especially when inefficient rotary suction cutters are used that cause vitreous 'winding', including anterior vitrectomy procedures via the limbus). This immediate or peroperative mechanism of GRT formation was excluded in all three patients by the routine practice of examination of the oral retina posterior to pars plana entry sites towards the end of the vitrectomy procedures and at early postoperative examinations.

Detachment of retained vitreous cortex in the months or years after surgery is a familiar sequel to central vitrectomy, and is occasionally complicated

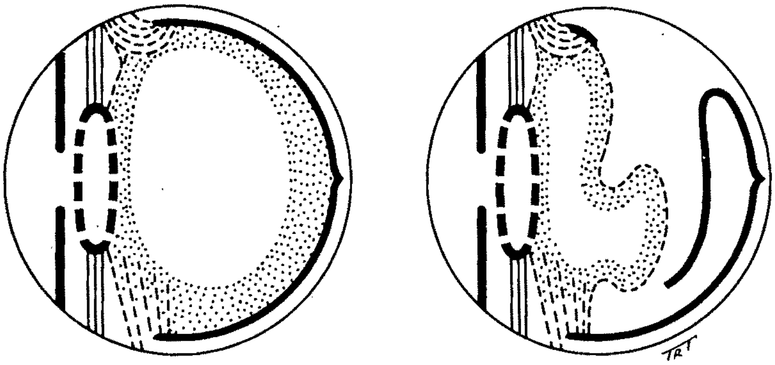

Fig. 1 Left: *Lacuna after central vitrectomy via the pars plana with basal gel incarceration.* Right: *Giant retinal tear formation after detachment of residual vitreous cortex.*

by formation of juxtabasal or postbasal flap tears or operculated tears owing to dynamic vitreoretinal traction. The GRTs in these three cases may represent an extreme variant of this process possibly related to undue vitreous incarceration in entry sites. In all three cases the site of the giant tear included a vitrectomy wound. Alternatively pre-existing or surgically induced retinal weakness at the posterior border of the vitreous base may be implicated. Whether GRTs occur after vitreous cortex detachment without vitreous base incarceration (for example, after limbal vitreolensectomy) is uncertain. Several such cases have been managed at our unit after referral, but it was not clear whether the GRTs developed at the time of vitreolensectomy or subsequently.

Other types of delayed retinal tearing secondary to basal gel incarceration in pars plana entry sites have been described.[4] Such juxtabasal tears may even follow posterior or 'complete' vitrectomy made possible by the occurrence of PVD prior to surgery (as is usually the case in vitrectomy for posterior segment pathology). However, giant breaks are not seen in these circumstances.

Vitreolensectomy is becoming an increasingly popular method of treating congenital cataracts because of the optical advantages over simple lens aspiration via the limbus.[5 6] Girard uses this method for most types of cataract.[7] However, the degree of prophylactic cryocoagulation of the peripheral retina appropriate after such procedures has seldom attracted much attention. The development of GRTs in these three reported cases has obvious implications for perhaps all eyes undergoing 'incomplete' vitrectomy (for example, anterior vitrectomy or central vitrectomy), especially via the pars plana. Carefully monitored cryotherapy is recommended across the demonstrable or presumed location of the posterior border of the vitreous base for 30° on each side of all pars plana entry sites, extended to 360° in selected cases.[8 9]

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References

1 Tolentino FI, Schepens CL, Freeman HM. *Vitreoretinal disorders*. Philadelphia; Saunders, 1976: 391.
2 Scott JD. Static and dynamic vitreous traction. *Trans Ophthalmol Soc UK* 1971; **91:** 175–87.
3 Cox MS, Schepens CL, Freeman HM. Retinal detachment due to ocular contusion. *Arch Ophthalmol* 1966; **76:** 678–85.
4 Michels RG. *Vitreous surgery*. St Louis: Mosby, 1981: 272, 399, 400.
5 Peyman GA, Raichand M, Goldberg MF. Surgery of congenital and juvenile cataract: a pars plicata approach with the vitreophage. *Br J Ophthalmol* 1978; **62:** 780–3.
6 Taylor D. Choice of surgical technique in the management of congenital cataract. *Trans Ophthalmol Soc UK* 1981; **101:** 114–7.
7 Girard LJ. Pars plana lensectomy by ultrasonic fragmentation. I: A versatile and simple technique for cataract removal. *Surv Ophthalmol* 1982; **27:** 96–104.
8 McLeod D. A retinal surgeon's view of congenital cataract surgery. *Aust J Ophthalmol* in press.
9 Jagger JD, Cooling RJ, Fison LG, Leaver PK, McLeod D. Management of retinal detachment following congenital cataract surgery. *Trans Ophthalmol Soc UK* 1983; **103:** 103–7.

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Glaucoma triple procedure of extracapsular cataract extraction, posterior chamber lens implantation, and trabeculectomy

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SUMMARY Thirty-four consecutive glaucoma triple procedures with a minimum follow up of six months have been shown to be effective and safe. Satisfactory control of the glaucoma was achieved in each case, and 91% of eyes were returned to an acuity of 6/12 or better. 1% sodium hyaluronate was found to be beneficial by preventing scleral or corneal collapse during surgery and ensuring an even filtration postoperatively without hypotony.

Glaucoma and cataract are often separated as surgical entities, for one requires a wound that leaks and the other a wound completely watertight. However, their frequent coexistence has led to a wealth of ideas as to how best to control the glaucoma and at the same time improve the vision. Many successful designs have been made for the operations to be combined,[1-5] but occasional over filtration may be associated with shallow anterior chamber, choroidal detachment, and peripheral anterior synechia, so that the introduction of simultaneous lens implantation could prove an unnecessary hazard. The consensus from lens implant surgeons is that chronic glaucoma is a relative contraindication to lens implantation, and that when it is indicated the glaucoma should be controlled prior to cataract surgery.[6] Some authorities believe this should be the approach even when lens implantation is not under consideration, provided the patient can withstand two procedures, and particularly as cataract surgery alone may prove more complicated in patients with glaucoma than in those without.[7] It is also known that intracapsular cataract extraction (ICCE) may lead to failure of a previously successful filtration procedure,[2,8,9] and that unoperated glaucoma can become more difficult to control in the aphakic eye.[10,11] Extracapsular cataract extraction (ECCE) may prove difficult because of a bound down or poorly dilating pupil. However, when ECCE is chosen a later trabeculectomy is likely to be as successful as if it were performed on a phakic eye, and there are no problems of vitreous possibly blocking the filtration site or adhering to the wound. Theoretically, therefore, when a combined procedure is considered trabeculectomy should have a higher incidence of success when combined with extracapsular than with intracapsular extraction.

1% sodium hyaluronate (Healonid) may contribute to the effectiveness of the combined procedure by preventing scleral or corneal collapse during surgery and by ensuring an even filtration postoperatively without anterior chamber shallowing.

So with these points under consideration this communication presents an improved single procedure for the treatment of cataract with glaucoma.

Material and methods

Thirty-four consecutive glaucoma triple procedures have been analysed with a minimum follow up of six months and a maximum follow up of four years (mean 14 months). All patients received trabeculectomy combined with ECCE. Six received a Boberg Ans posterior chamber implant, and 28 received a Sinskey or Pearce flexible loop posterior chamber implant. All eyes had intraocular pressures persistently above 21 mmHg before treatment, and all eyes had visual acuity reduced to less than 6/24 because of cataract. The 34 eyes of 33 patients were divided into the following three groups: (1) eight cases of ocular hypertension or preglaucoma (OHT) showing no field defect and a cup disc ratio of less than 0·65; (2) 21 cases of chronic simple (open-angle) glaucoma (CSG) with a field defect in the operated or

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fellow eye and a cup disc ratio of 0·65 or greater in the operated eye; (3) five cases of chronic angle closure glaucoma (CACG).

Two eyes from group (2) and four from group (3) had received previous glaucoma surgery. Two had had previous filtration procedures, and four had had previous peripheral iridectomies, including one eye that had also received a subsequent trabeculectomy. All eyes that had suffered previous glaucoma surgery had small bound down pupils from formation of posterior synechiae. There were no cases of secondary glaucoma.

Table 1 shows the age range, the mean intraocular pressures at presentation, and the mean intraocular pressures prior to surgery after various combinations of pilocarpine, timolol, neutral adrenaline and guanethidine. Despite this topical therapy 16 eyes had pressures persistently above 21 mmHg.

The glaucoma triple procedure comprised: (1) A fornix based conjunctival flap. (2) A two-thirds depth scleral incision 5 mm of which was placed 4 mm posterior to the limbus for the trabeculectomy, 7 mm placed 1 mm posterior to the limbus for later insertion of the implant. (3) The outer trabeculectomy flap was dissected into the cornea and extended the entire length of the incision so that the part not used for trabeculectomy formed a two-plane step. (4) The base incision for the trabeculectomy 2·5 mm posterior to the limbus. (5) A 1 mm stab incision and anterior capsulotomy under sodium hyaluronate. (6) Completion of the trabeculectomy. In those eyes with bound down pupils stage 6 was done before stage 5 with conversion of peripheral iridectomy to broad (sector) iridotomy and inferior sphincterotomy, in order to facilitate the capsulotomy. Sodium hyaluronate was used not only to protect intraocular tissues from inadvertent trauma but also to prevent scleral or anterior chamber collapse during surgery. (7) Completion of the 12 mm step incision. (8) Removal of a disc of anterior capsule with Kelman McPhearson forceps through a medium of sodium hyaluronate. (9) Injection of sodium hyaluronate behind the lens nucleus and extraction of the nucleus by scleral depression without counterpressure or reflection of the cornea. (10) Non-automated aspiration/irrigation of residual lens cortex after placement of a central direct suture. (11) Closure of the trabeculectomy flap to one side of the direct suture. (12) Intraocular lens insertion to the other side of the direct suture through a medium of sodium hyaluronate without reflecting the cornea. (13) Wound closure with three further direct scleral sutures of 10/0 nylon. (14) Injection of sodium hyaluronate under trabeculectomy flap. (15) Securing of the apron of conjunctiva with a limbal 8/0 Vicryl suture at each end of the wound and buried knot. (16) Subconjunctival injection of Depo-Medrone (methylprednisolone acetate) with Soframycin (framycetin sulphate) and topical application of timolol maleate.

Table 1 *Age and preoperative intraocular pressure*

	Eyes	*Age range (yr)*	*Presenting IOP (mmHg)*		*Preoperative IOP (mmHg)*	
			Mean	*Range*	*Mean*	*Range*
(1) OHT	8	60–80	26	23–30	21	17–26
(2) CSG	21	65–84	30	23–56	22	16–28
(3) CACG	5	66–79	42	26–60	25	20–32

Results

Table 2 shows the movement of postoperative intraocular pressure. The majority of eyes underwent applanation tonometry at eight hours, all at 22 hours. Six (21%) of the cases in groups 1 or 2 were found to have pressures raised above 30 mmHg during the first 24 hours, but by the third day there were no high pressures. By six months all pressures in these two groups were below 20 mmHg though for three eyes timolol drops had had to be restarted, and there was a net mean fall of 6·1 mmHg since surgery. Despite several cases of moderately severe optic atrophy 26 of the 29 eyes were seeing 6/9 or better. The other three eyes suffered from macular degeneration.

The five cases of CACG were expected to prove more difficult to treat. Intraocular pressures were all uncontrolled despite treatment, and four had bound down pupils from previous surgery. However, all had a satisfactory response to treatment with total control of intraocular pressure. All were seeing at six months

Table 2 *Postoperative intraocular pressure (mmHg)*

	First 24 hours		*Third day*		*Six months*		*Mean fall from preoperative level*
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*	
(1) OHT	17	7–32	15	12–20	14	12–16	6·3 mmHg
(2) CSG	24·5	5–46	15·9	11–25	15·8	12–19*	6·0 mmHg
(3) CACG	15	12–18	15·4	12–23	14	12–16	11·0 mmHg

*Three eyes required additional timolol drops.

6/12 or better and showed a mean fall in intraocular pressure of 11 mmHg.

LONG TERM FOLLOW UP

Thirteen eyes have been followed up for more than two years and four for more than three. All these eyes at the final point of follow up were seeing 6/12 or better, though one had required a posterior capsulotomy to achieve this. The intraocular pressure has been maintained at below 19 mmHg in all, 11 requiring no additional medication and two requiring additional timolol drops. Of the other 21 eyes one required a capsulotomy at six months because of capsule fibrosis, and three eyes had received primary capsulotomy. Thus 29 eyes have so far maintained a clear posterior capsule. It should be expected that some of these will require capsulotomy at a future date, but this is not a difficult procedure even with a posterior lens in situ. The posterior capsule is not therefore regarded as a problem but rather as an aid to surgery, as it ensures stability of the implant and of the posterior segment of the eye.

COMPLICATIONS

There were no cases of overfiltration with ocular hypotony, choroidal detachment, or shallowing of the anterior chamber. Apart from minor surgical hyphaemas there was one eye with secondary hyphaema that lasted four weeks but recovered 6/9 vision. Three lens implants were found to decentre upwards toward the trabeculectomy site but not far enough to trouble the patient with a crescent of aphakic vision. There were no cases of implant subluxation or postoperative corneal oedema.

Three eyes developed pupil trap (or creep). Starting with adherence of the pupil margin to the posterior capsule the pupil was found slowly to creep behind the lens implant as already described in glaucoma eyes by Rock and Rylander.[12] Two eyes showed 'against the rule' astigmatism higher than +2·5 D, of +4·0 D and +5·0 D respectively, with the axis corresponding to bleb formation at the trabeculectomy site.

Discussion

The above complications signify an increased morbidity after this operation compared with standard extracapsular surgery, possibly owing to the unidirectional flow of aqueous and an increased tendency to low grade uveitis. But this is outweighed by the advantages of combining the operations into one procedure, and there were no cases of visual loss in the short term resulting from a complication of surgery. The low grade uveitis signified by mild ciliary injection with minimal cellular activity in the anterior chamber persisting in a few eyes for up to eight weeks was not associated with any failure of filtration. Neither was the presence of the implant found in any way to compromise the filtration bleb or the resulting visual acuity.

The absence so far of any of our cases resulting in inadequate glaucoma control is encouraging and, in agreement with others,[4 10 11] suggests a preference for trabeculectomy rather than cyclodialysis during the combined procedure. Galin and Baras[13] showed that after ICCE and cyclodialysis 40% of patients required additional medication, and that in 10% of eyes the glaucoma remained uncontrolled. In Montgomery and Gills's[8] large series of ECCE/cyclodialysis/posterior chamber implant triples 38% of patients required additional glaucoma medication before one year had passed, and 13% remained uncontrolled, but of those that were controlled there was no attenuation with time over a three-year period. 3% of patients had required surgical reformation for flat anterior chamber in the early postoperative period.

The incidence of shallow or flat anterior chamber after the combined procedure of intracapsular extraction and trabeculectomy, though absent in Rich's series,[4] has been variously reported by others as being between 7% and 16%.[7 10 14 15] This complication seems to be avoided by placement of Healonid (sodium hyaluronate, sodium chloride, sodium phosphate dihydrate, sodium acid phosphate monohydrate) in the anterior chamber and under the trabeculectomy flap to ensure an even filtration in the early postoperative period. The manoeuvre appeared to be successful in preventing a shallow chamber or any complication from ocular hypotony. However, six eyes sustained a high intraocular pressure during the first 24 hours after operation. This is a phenomenon already experienced without the use of Healonid,[4 11 15] and to prevent compromise of the optic nerve it is important to guard against it and to continue timolol drops for at least two days after surgery.

The choice of ECCE over ICCE during the combined procedure seems to confer the following advantages: (1) theoretically better control of the glaucoma, since the eye behaves like a phakic eye, and there will be no possibility of vitreous adhering to the filtration site; further, if a second filtration procedure were to become necessary at a future date, for the same reasons, this would be less hazardous after ECCE than after ICCE; (2) the facility to insert a purely posterior chamber implant without the need for polypropylene loops anteriorly or iris fixation sutures as would be necessary after ICCE; (3) better visual results as has been suggested before.[16] The fact that 91% of these eyes had a postoperative acuity of 6/12 or better is partly explained by the absence of eyes with near absolute glaucoma. However, consideration must also be given to the fact that the presence of an intact lens capsule and absence of hypotony both contribute to a reduction of macular oedema. Other authors using the ICCE technique give a postoperative 6/12 acuity incidence varying between 42% and 66%.[4,5,7,9,10,14,15] Clearly there must be considerable variation in any given series over the health of individual optic nerves, but an already compromised nerve cannot be helped by even mild (and often undiagnosed) macular oedema. It is significant that Montgomery and Gills,[8] who used the ECCE technique, alone gave a 6/12 or better incidence at one year of over 80%.

The single problem presented by ECCE concerned the bound down or poorly dilating pupils. These eyes were managed with radial iridotomies and inferior sphincterotomies but without secondary iris suturing, which was considered a possibly hazardous extra manipulation. A possible disadvantage here is a crescent of aphakic vision in those eyes with a wide palpebral aperture. However, among these particular patients there were no complaints of diplopia or pupillary abnormality.

CONCLUSION

The results suggest that with the facility of sodium hyaluronate this glaucoma triple procedure is both safe and effective, and that the inclusion of a posterior chamber implant does not jeopardise either the glaucoma control or the visual improvement.

References

1 Harrington DO. Cataract and glaucoma. Management of the coexistent conditions and description of a new operation combining lens extraction with reverse cyclodialysis. *Am J Ophthalmol* 1966; **61:** 1134–8.

2 Galin MA, Baras I, Sambursky J. Glaucoma and cataract. A study of cyclodialysis—lens extraction. *Am J Ophthalmol* 1969; **67:** 522–7.

3 Witmer R. Kombinierte Glaukom-Katarakt operation. *Ophthalmologica* 1972; **165:** 203–5.

4 Rich W. Cataract extraction with trabeculectomy. *Trans Ophthalmol Soc UK* 1974; **94:** 458–67.

5 Eustace P, Harun AQSM. Trabeculectomy combined with cataract extraction. *Trans Ophthalmol Soc UK* 1974; **94:** 1058–63.

6 Richardson KT. Glaucoma and pseudophakia. In: Rosen ES, Haining WH, Arnott EJ, eds. *Intraocular lens implantation.* St Louis: Mosby, 1984: 619–21.

7 Spaeth GL. Management of patients with conjoint cataract and glaucoma. *Ophthalmic Surg* 1980; **11:** 780–3.

8 Montgomery D, Gills JP. Extracapsular extraction, lens implantation and cyclodialysis. *Ophthalmic Surg* 1980; **11:** 343–7.

9 Shields MB. Combined cataract extraction and glaucoma surgery. *Ophthalmology* 1982; **89:** 231–7.

10 Johns GE, Layden WE. Combined trabeculectomy and cataract extraction. *Am J Ophthalmol* 1979; **88:** 973–81.

11 Witmer R, Rohen JW. Combined cataract glaucoma operation. *Trans Ophthalmol Soc UK* 1976; **96:** 256–61.

12 Rock RL, Rylander HG. Spontaneous iris retraction after extracapsular extraction and posterior lens implantation in patients with glaucoma. *Am Intraocular Implant Soc J* 1983; **9:** 45–7.

13 Galin MA, Baras I. Combined cyclodialysis cataract extraction: a review. *Ann Ophthalmol* 1975; **7:** 721–9.

14 Edwards RS. Trabeculectomy combined with cataract extraction: a follow up study. *Br J Ophthalmol* 1980; **64:** 720–4.

15 Jerndal T, Lundstrom M. Trabeculectomy combined with cataract extraction. *Am J Ophthalmol* 1976; **81:** 227–31.

16 Percival SPB, Anand V, Das SK. Prevalence of aphakic retinal detachment. *Br J Ophthalmol* 1981; **67:** 43–5.

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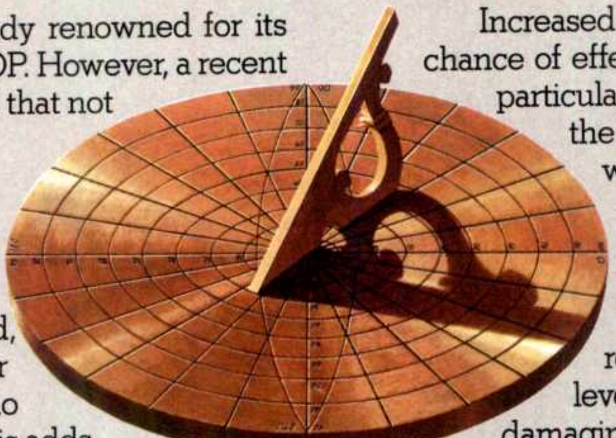

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REFERENCES
1. Sponsel, W. E., *et al., Brit. J. Ophthal.*, 1983, 67, 220.
2. Norell, S. E., *Amer. J. Ophthal.*, 1981, 92, 727.
3. MacKean, J. M., and Elkington, A. R., *Brit. J. Ophthal.*, 1983, 67, 46.
4. Reynolds, P. M., *Glaucoma*, 1982, 262.
5. Willcockson, J., and Willcockson, T., *Glaucoma*, 1982, 155.

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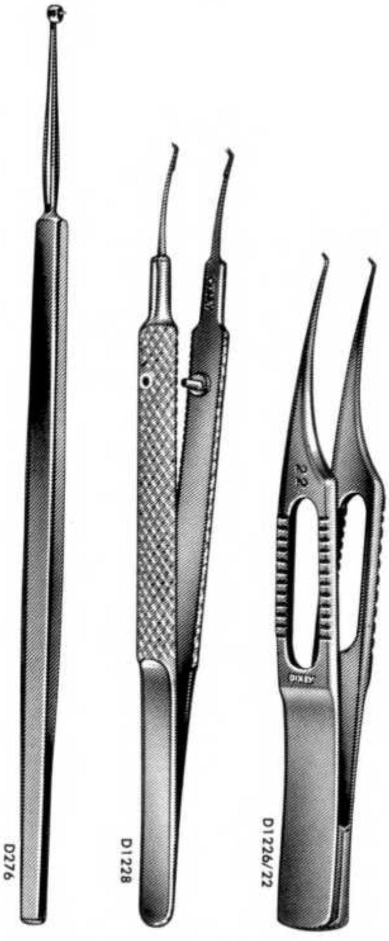

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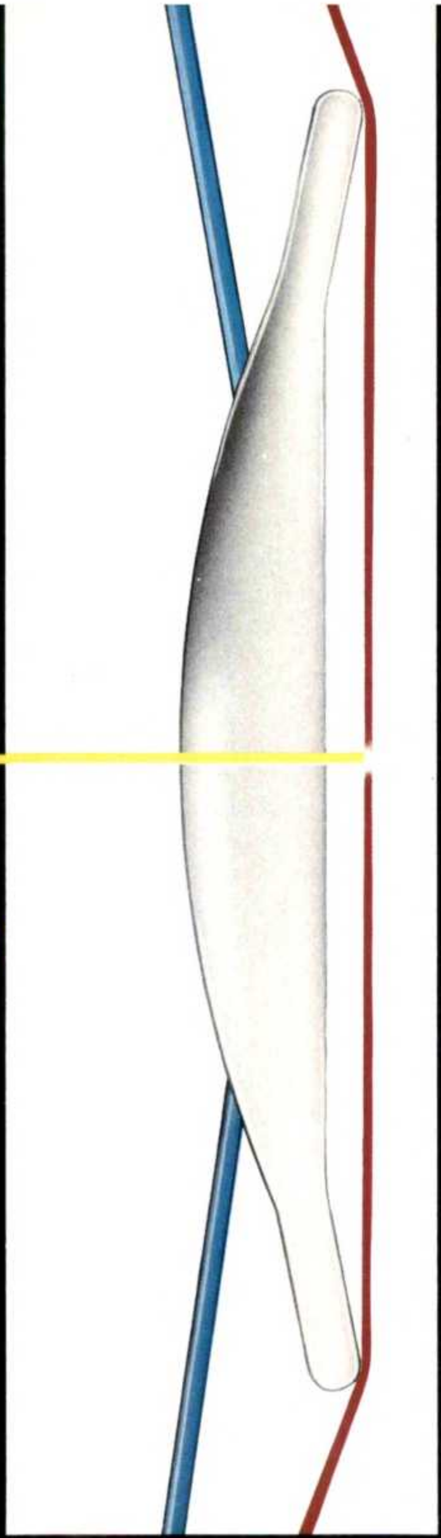

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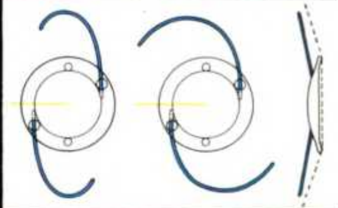

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Anterior chamber angle in the exfoliation syndrome

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SUMMARY The gonioscopic findings of 76 patients with the exfoliation syndrome were reviewed. A high frequency of narrowness of the anterior chamber (AC) angle was found (32%). 18% had angles considered occludable, and 14% had obvious angle-closure glaucoma as shown by the presence of peripheral anterior synechias (PAS). Increased pigmentation of the posterior trabecular meshwork (PTM) was noted in all cases. When this pigmentation was markedly asymmetrical, unilateral exfoliation with glaucoma was common in the more pigmented eye. In addition heavy angle pigmentation in the absence of exfoliation was noted in the fellow eye of patients with characteristic exfoliated material in the other eye. Increased pigmentation of the PTM may be the earliest detectable sign of the exfoliation syndrome (ES). The clinical significance of our estimating PTM pigmentation at the 12 o'clock position is discussed. In view of the accelerated optic nerve damage associated with the development of glaucoma secondary to ES, routine estimation of the pigmentation of the PTM at 12 o'clock is recommended in the hope of early detection of cases of otherwise inapparent ES.

The exfoliation syndrome (ES) is a condition in which a whitish-grey material of uncertain origin is deposited on surfaces within the anterior segment of the eye: lens, iris, zonules, and ciliary processes. The ES is usually recognised by the appearance of these deposits on the anterior surface of the pupil margin. The exfoliated material may be present on the corneal endothelium and in the angle of the anterior chamber (AC). This exfoliated material has a multifocal origin. It may be the result of an abnormal basement membrane synthesis by aging cells.[1]

Atrophy of the pupil margin and adjacent iris transillumination defects are frequently found.[2] Increased trabecular pigmentation has been described and is believed to be a result of depigmentation of the iris.[3] A wavy, pigmented line present on the corneal endothelium in the inferior portion of the angle anterior to Schwalbe's line has been described by Amalric *et al.*[4] and Sampaolesi[5] and is so characteristic that it strongly suggests the presence of ES. That glaucoma is associated with ES has been well demonstrated, though estimates of the closeness of the relationship vary widely.[6 7]

A relationship between angle-closure glaucoma and ES has been mentioned, but authors in the past appear to believe that the relationship is only coincidental.

Materials and methods

The source of the patients in this study was a hospital-based private practice. The records of all patients diagnosed as having ES who were examined on initial or return visits between January 1982 and May 1983 were studied retrospectively. All patients had optic disc drawings or photographs taken, applanation tonometry, visual field testing, and Zeiss four-mirror pressure gonioscopy.[8] A diagnosis of ES was made when the characteristic deposits of exfoliated material were seen on the pupil margin or anterior surface of the lens. Glaucoma was diagnosed by the presence of characteristic glaucomatous nerve damage and/or field loss associated with raised intraocular pressure (IOP). Every case was examined by one of the authors (G.L.S.). The analysis of data and a re-examination of selected cases were done by P.K.W. The following characteristics were recorded: (1) Wills Eye Hospital angle configuration grading the angular approach to angle recess, curvature of the peripheral iris, and position of iris insertion.[9 10] (2) Pigmentation of PTM at 12 o'clock graded 0-nil to 4+

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severe. (3) Pigment deposition in the inferior angle recess (at 6 o'clock). (4) Presence or absence of peripheral anterior synechias (PAS).

The records of all 88 patients coded as having ES were reviewed. Twelve cases were excluded because of extraneous factors that would influence the angle appearance. Exclusions include: three cases with previous trauma causing angle recession, one case with anterior uveitis, two cases with previous laser trabeculoplasty, and six cases with previous intraocular surgery.

To compare these findings with a glaucomatous population 150 records were chosen randomly for review, all cases having been examined during the same time interval and in the same office by the same examiner (G.L.S.). All patients with secondary glaucoma, previous intraocular surgery, trauma, or other eye disease were excluded. To achieve age matching, patients less than 58 years old were also excluded.

Results

Seventy six patients were included in this study. Seventy three had glaucoma, and three showed no evidence of glaucoma. The three patients with no evidence of glaucoma had bilateral ES and open angles. Deposits of exfoliated material were seen on the pupil margin in 24 patients and on the anterior lens capsule in 67 patients. The frequency of open, narrow, and closed angles is shown in Table 1.

Forty eight patients (64%) had 3+ or more pigmentation of the PTM (Fig. 1). Twenty one (27%) had 2+ pigmentation and seven (9%) less than 2+ pigmentation (Table 2). Of the 76 patients 16 showed marked pigment asymmetry (pigment grading different by more than two units). Of these 16, 13 (81%) had significantly more glaucomatous damage in the eye with the heavier pigmentation, while three (19%) showed no difference in the degree of glaucomatous damage.

Of the 76 patients none was seen in whom the eye with less pigmentation showed more glaucomatous damage than its more heavily pigmented fellow. In 75 of the 76 patients pigment deposition at 6 o'clock was greater than the pigmentation of the PTM at 12 o'clock. The characteristics of the 80 patients who satisfied the criteria for selection as an age matched group of primary glaucoma controls are shown in Table 3.

Table 1 *Relation between width of angle and ES*

Angle	*No of cases*	*Bilateral ES+*	*Unilateral ES+*
Open-angle*	51 (68%)	34	17
Narrow-angle†	14 (18%)	3	11
Angle-closure‡	11 (14%)	6	5
Total	76	43	33

*Open-angle. An angle width greater than 25° with little curvature of the iris (r).

†Narrow-angle. An angle width less than 25° with the iris curved anteriorly (s).[25]

‡Angle-closure. Defined as such by the presence of peripheral anterior synechias (PAS).

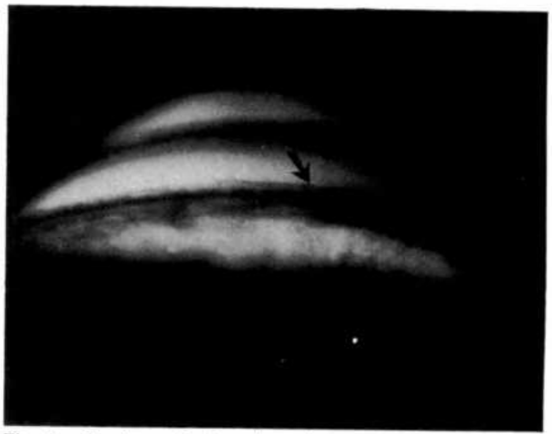

Fig. 1 *Gonioscopic view shows intense pigmentation of the posterior trabecular meshwork and presence of a Sampaolesi line (arrowed) characteristic of the exfoliation syndrome.*

Table 2 *Pigmentation of the posterior trabecular meshwork at the 12 o'clock position* in 76 cases of ES*

Glaucoma	*No of cases*	*Pigment of 3+ or more*	*Pigment of 2+*	*Pigment of less than 2+*
No glaucoma	3	1	2	0
Open-angle	48	29	14	5
Narrow-angle	14	10	3	1
Angle-closure	11	8	2	1

*In cases where pigmentation was asymmetric the more darkly pigmented eye is recorded.
Average age 70 years. Sex ratio 33 men: 43 women.

Table 3 *Characteristics of an age matched population of glaucoma cases without the exfoliation syndrome or other secondary glaucoma*

	No of cases
Diagnosis	
Primary open-angle glaucoma	63
Glaucoma with narrow but open angles	11
Primary angle-closure glaucoma	6
Pigmentation of posterior trabecular meshwork at 12 o'clock	
3+ or more	7 (9%)
2+	14 (17%)
Less than 2+	59 (74%)

Average age 68 years.
Sex ratio 32 men: 48 women.

Of 31 patients with bilateral ES and bilateral open-angle glaucoma only two (6%) showed marked pigment asymmetry of the PTM at 12 o'clock. Of nine patients with unilateral ES and bilateral open-angle glaucoma three (30%) showed marked asymmetry, and of the eight patients with unilateral ES and ipsilateral unilateral open-angle glaucoma six (86%) showed marked pigment asymmetry.

Discussion

AC DEPTH AND ANGLE CLOSURE

The accepted view that the AC angle in cases of ES is generally open, and the AC of normal depth[2 11-14] was challenged by the report of Layden and Shaffer[15] citing an incidence of narrow angles in 23% of their cases of ES. In the normal elderly population narrow angles occur in only 4% of patients,[9 16] and less than 1% of the general population is thought to have critically narrow angles.[17 18] This corresponds with estimates of the frequency with which primary angle closure occurs clinically.[9] In other reported series of ES the incidence of angle closure is generally 4% or less,[12 13 19 20] whereas 25 (32%) of our 76 patients had narrow or closed angles.

We believe the high incidence of closed angles in our population may reflect the increased visualisation of PAS made possible by indentation gonioscopy[8] performed routinely on all our patients. The much higher incidence of narrow and closed angles in our patients with ES compared with our primary glaucoma control group makes it unlikely that we are describing a drug-induced effect. It should be noted that treatment with ecothiopate has been thought to be related causally to the occurrence of angle closure glaucoma in patients with ES.[15] In our series of cases of ES only one was receiving echothiopate, and in this case the angle was narrow but open. None of the other 75 patients was receiving this drug (Fig. 2). We believe that the association of a narrow AC angle and ES is real, and that early reports indicating no association between them represent incomplete observation. A possible explanation for this narrow angle has been given by Herbst, who believes that it relates to pupil block.[21]

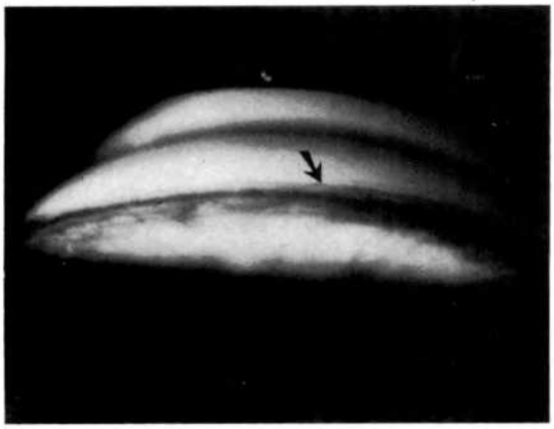

Fig. 2 *Narrow anterior chamber angles are more common in patients with the exfoliation syndrome than in age matched controls. This appears not to be merely a factor of the use of miotics but an aspect of the disease itself.*

Special attention should be paid to the monitoring of the AC angle of patients with ES in order to prevent the development of angle closure glaucoma, a condition to which patients with ES are predisposed.

PIGMENTATION

A densely pigmented trabecular band is regarded as a sign of ES.[2 19 22] However, few reports of ES actually record their assessment of pigmentation, and, in those that do, incidences of 35% to 70% of no remarkable TM pigmentation are found.[12 15] Furthermore ES occurs in the elderly,[15 19] and pigmentation of PTM and inferior angle recess have been shown to increase with age.[9 18] Reports of TM pigmentation in the ES would therefore be more instructive if the site of assessment of TM pigmentation had been given.

It has been shown that pigmentation of PTM is of most diagnostic significance if assessed at the 12 o'clock position, and at this position 65·8% of normal eyes showed no pigmentation of their PTM. Only 2·5% of normal eyes showed pigment grading 3+ or more (average age 70 years).[9]

Table 4 clearly shows that there is a much greater incidence of dense pigmentation of the PTM in patients with ES than in normals or cases of primary glaucoma.

A significant relationship between increased angle pigmentation and glaucoma has been affirmed by some authors[12 19 23] though denied by others.[15] In our study marked pigmentation of the PTM (when assessed at 12 o'clock) appears to be part of the ES and to be related to the presence of glaucoma. Furthermore as a prognostic factor, when marked pigment asymmetry was found, 81% of the more heavily pigmented eyes showed the more severe glaucoma.

Table 4 *Pigmentation of posterior trabecular meshwork at 12 o'clock*

Pigmentation of PTM	*Normal cases*	*Primary glaucoma cases*	*Glaucoma with ES cases*
Less than 2+	87·9%	74%	9%
2+	9·5%	17%	27%
3+ or more	2·5%	9%	64%

Richardson and Epstein have noted that the trabecular cells of eyes with ES appear normal and do not contain exfoliated material.[24] They found the major pathology to be destruction of Schlemm's canal and accumulation of exfoliated material in the juxtacanalicular region. Accumulation of pigment was minimal. In contrast, studies of pigmentary glaucoma show that pigment deposition within the cells of the trabecular region is prominent and appears to play a significant pathogenetic role in the development of glaucoma.[25-27] Further histological studies are needed in this regard.[28]

DIAGNOSTIC VALUE OF PIGMENTATION

27% of our ES showed a 2+ pigmentation of PTM and 64% 3+ or more when pigment was assessed at the 12 o'clock position (total 91%). These results indicate that increased pigmentation of PTM is a reliable sign of ES. The diagnostic pupil border deposits of ES were only visible in 32% of our patients and therefore represent a much less frequently seen sign of the ES than increased pigmentation of PTM.

We observed the development of lens or pupil deposits of exfoliated material in six patients who were not thought to have ES when first seen, because no exfoliated material was observed. Four of these were recorded at the initial visit as having pigmentation of the PTM of grade 2+ or more.

The demonstration by cycloscopy of exfoliated deposits on zonules and ciliary processes in more than half the fellow eyes of unilateral cases of ES shows that exfoliated material may be present, even if lens or iris deposits cannot be seen.[29] In the absence of cycloscopy, intense pigmentation of the PTM may be the earliest sign of ES actually predating the development of visible 'dandruff.'

As has been found with other studies, when glaucoma is associated with ES, the IOP is difficult to control, and there is a high incidence of severe optic nerve damage.[30 31] Of the 76 patients in our series 51 eyes showed severe optic nerve damage associated with gross glaucomatous visual field loss. Early detection of the first sign of glaucoma in a patient with ES is important, so prompt therapy may be given.

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References

1 Eagle RC Jr, Font RL, Fine BS. The basement membrane exfoliation syndrome. *Arch Ophthalmol* 1979; **97:** 510.

2 Aasved H. Incidence of defect in the pigmented pupillary ruff in eyes with and without fibrillopathia epitheliocapsularis. *Acta Ophthalmol (Kbh)* 1973; **51:** 710.

3 Sugar HS, Harding C, Barskey O. Exfoliation syndrome. *Ann Ophthalmol* 1976; **8:** 1165.

4 Amalric P, Sampaolesi R, Bessou P. Early diagnosis and heredity of pseudocapsular exfoliation. *Bull Soc Ophthalmol Fr* 1960; **5–6:** 341–50.

5 Sampaolesi R. New gonioscopic signs in congenital glaucoma of late onset. *Modern problems in ophthalmology*. New York: Karger. **6:** 106–23. First South American Glaucoma Symposium, Bariloche, 1966.

6 Aasved H. Intraocular pressure in eyes with and without fibrillopathia epitheliocapsularis. *Acta Ophthalmol (Kbh)* 1971; **49:** 601–10.

7 Kozart DM, Yanoff M. Intraocular pressure status in 100 consecutive patients with exfoliation syndrome. *Ophthalmology* 1982; **89:** 214–8.

8 Forbes M. Gonioscopy with corneal indentation. *Arch Ophthalmol* 1966; **76:** 488–92.

9 Spaeth GL. The normal development of the human anterior chamber angle: A new system of descriptive grading. *Trans Ophthalmol Soc UK* 1971; **91:** 709–59.

10 Spaeth GL. Gonioscopy: Uses old and new. The inheritance of occludable angles. *Ophthalmology* 1978; **85:** 222–32.

11 Layden WE. Exfoliation syndrome. In: Rich R, Shields MB, eds. *The secondary glaucomas*. St Louis: Mosby, 1982: 99–120.

12 Tarkkanen A. Pseudoexfoliation of the lens capsule. (A. clinical study of 418 patients with special reference to glaucoma, cataract, and changes of the vitreous). *Acta Ophthalmol (Kbh)* 1962; **71:** 56–84.

13 Lowe RF. Primary angle-closure with capsular exfoliation of the lens. *Br J Ophthalmol* 1964; **48:** 492–4.

14 Bartholomew RS. Anterior chamber depths in eyes with pseudoexfoliation. *Br J Ophthalmol* 1980; **64:** 322–7.

15 Layden WE, Shaffer MD. Exfoliation syndrome. *Am J Ophthalmol* 1974; **78:** 835–41.

16 Kuribayashi T, Segawa K. The iridocorneal angle of old age: A correlated gonioscopy and scanning electron microscopy. *Folia Ophthalmol Jpn* 1980; **31:** 182–7.

17 Kolker AE, Hetherington J, eds. *Becker and Shaffer's diagnosis and therapy of the glaucomas*. St Louis: Mosby, 1976: **47:** 183.

18 François J. *La gonioscopie*. Fonteyn: Louvain, 1948: 58–60.

19 Roth M, Epstein DL. The exfoliation syndrome. *Am J Ophthalmol* 1980; **89:** 477–81.

20 Gnanadoss AS, Parasuraman A. Pseudoexfoliation and narrow angle glaucoma (case reports). *Orient Arch Ophthalmol* 1972; **10:** 55–7.

21 Herbst RW. Angle-closure glaucoma in a patient with pseudoexfoliation of the lens capsule. *Ann Ophthalmol* 1976; **8:** 852–8.

22 Dunbar-Hoskins H. Part 5. In: Heilmann K, Richardson T. eds. *Glaucoma, conceptions of a disease*. Philadelphia: Saunders, 1978: 386.

23 Madden JG, Crowley MJ. Factors in the exfoliation syndrome. *Br J Ophthalmol* 1982; **66:** 432–7.

24 Richardson TM, Epstein DL. Exfoliation glaucoma: A quantitative perfusion and ultrastructural study. *Ophthalmology* 1981; **88:** 968–80.

25 Rodrigues MM, Spaeth GL, Weinreb S, *et al.* Spectrum of trabecular pigmentation in open-angle glaucoma: A clinicopathologic study. *Trans Am Acad Ophthalmol Otolaryngol* 1976; **81:** 258–76.

26 Richardson TM, Hutchinson BT, Grant WM. The outflow tract in pigmentary glaucoma: a light and electron microscopy study. *Arch Ophthalmol* 1977; **95:** 1015–25.

27 Petersen HP. Can pigmentary deposits on the trabecular meshwork increase the resistance of the aqueous outflow? *Acta Ophthalmol (Kbh)* 1969; **47:** 743–9.

28 Haddad R, Strasser G, Heilig P, *et al.* Decompensation of chronic open-angle glaucoma following mydriasis-induced pigmentary dispersion into the aqueous humour: A light and

electron microscopic study. *Br J Ophthalmol* 1981; **65:** 252–7.

29 Mizuno K, Muroi S. Cycloscopy of pseudoexfoliation. *Am J Ophthalmol* 1979; **87:** 513–8.

30 Olivus E, Thorburn W. Prognosis of glaucoma simplex and glaucoma capsularis. *Act Ophthalmol (Kbh)* 1978; **50:** 921–34.

31 Aasved H. The frequency of optic nerve damage and surgical treatment in chronic simple glaucoma and capsular glaucoma. *Acta Ophthalmol (Kbh)* 1971; **49:** 581–600.

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A randomised prospective study* on treatment of central retinal vein occlusion by isovolaemic haemodilution and photocoagulation

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SUMMARY Thirty eight patients with ischaemic and non-ischaemic central retinal vein occlusion were evaluated for the effect of isovolaemic haemodilution. They were allocated at random to a haemodilution group (19 patients, panretinal photocoagulation and isovolaemic haemodilution) and a control group (19 patients, panretinal photocoagulation). Haematocrit was lowered in steps to 30 to 35% in the haemodilution group by repeated exchanges of whole blood for plasma and dextran (MW 40 000) and kept at this level for a period of six weeks. The haemodilution did not lead to serious complications. Three months after starting the treatment eight of 19 patients with haemodilution showed a better visual acuity, whereas only one of 19 control patients had improved. Seven of 17 patients with haemodilution, but only one of 17 control patients, retained a better visual acuity after one year. In the haemodilution group there were fewer patients with macular fibrosis and more with only minor foveal changes. The haemodilution seems to be more effective in patients with ischaemic than with non-ischaemic central retinal vein occlusion. It is concluded that isovolaemic haemodilution improves the visual outcome of patients with central retinal vein occlusion, probably mediated by enhanced retinal blood flow.

There has been little change in the prognosis for visual acuity (VA) of the eye after central retinal vein occlusion (CRVO) during the past decades. Definite therapeutic effects have been achieved with the use of panretinal photocoagulation to prevent neovascular glaucoma in ischaemic CRVO.[1-3] An effective medical treatment is lacking.[4] The promising fibrinolytic therapy[5 6] has been abandoned by Kohner[7] because of its risk of vitreous haemorrhage, but it is still applied by others.[8]

The pathogenesis of CRVO is still not completely clear. There is controversy as to the primary event[9-11] of whether CRVO alone, or a transitory central retinal artery occlusion, leads to outflow obstruction with a rise in intravascular pressure, leakage of retinal capillaries, and expulsion of red cells. This might cause a local increase in blood viscosity by enhanced haematocrit and low shear rates, thus strengthening the vicious circle to stasis until at least a progressive ischaemic capillaropathy is produced. Furthermore, Ring *et al.*[12] detected a higher whole blood and plasma viscosity in patients with CRVO. This finding was corroborated by Trope *et al.*[13]

If increased viscosity is a factor promoting ischaemia, then reducing viscosity to normal or lower levels for weeks or months after the onset of venous occlusion might at least moderate retinal ischaemia and other sequelae of CRVO.

Recent work in man has shown that, after reduction of haematocrit values (and thus reduction in viscosity), cerebral blood flow can be improved.[14] Studies on retinal blood flow in pigs have shown an increase in blood flow when whole blood viscosity was reduced by isovolaemic haemodilution.[15 16] A pilot open study on isovolaemic haemodilution in CRVO by one of us[17] yielded very promising results

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*Preliminary results were presented at the 80th meeting of the Deutsche Ophthalmologische Gesellschaft and at the 1983 ARVO Meeting in Sarasota, USA.

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concerning visual acuity. However, the new therapeutic regimen did not prevent neovascular glaucoma. Panretinal photocoagulation has been a routine procedure in our hospital in most patients with CRVO,[18] and, since it is a well known procedure for prevention of retinal neovascularisation,[1-3] we decided to combine isovolaemic haemodilution with photocoagulation.

The study was designed as a prospective randomised trial to evaluate the efficacy of isovolaemic haemodilution in patients with ischaemic and non-ischaemic CRVO after panretinal photocoagulation.

Patients and methods

All patients over 40 years old with recent central venous occlusion (less than four months duration of symptoms) referred to our hospital between 1 November 1980 and 12 December 1982 were considered for the randomised, controlled, prospective trial.

Patients with systemic diseases (congestive heart failure despite treatment, renal and respiratory insufficiency of the pink puffer type, anaemia below 38% packed cell volume (PCV), thrombocytosis above 450×10^9/l, insufficient clarity of media, pre-existing macular disease, and psychosocial problems, which would not allow long term follow up, were excluded from the study (Table 1). In addition we did not treat patients with mild non-ischaemic CRVO without macular oedema whose visual acuity was above 6/7·5.

One of us (H.R.A.) took a thorough medical history and made a clinical examination of all patients. They were then referred for systemic evaluation including ECG, *x*-ray of the chest, and Doppler sonography of the supra-aortic vessels. If necessary an extended cardiovascular assessment (that is, 24 h ECG, echocardiogram, etc.) was done.

Blood was collected by standard laboratory methods to determine the values for the following: haemoglobin, haematocrit (PCV), blood film, ESR, platelet count, partial thromboplastin time, prothrombin time, serum creatinine, Na, K, blood glucose, serum cholesterol and triglyceride levels, uric acid, liver function, and serum protein electrophoresis.

Table 1 *Exclusion criteria for patients with CRVO*

	No of patients
Patients presenting with CRVO	53
Total excluded	15
Anaemia	1
Congestive heart failure	2
Respiratory insufficiency	1
No follow up possible	3
Ophthalmological reasons*	4
Age <40 years	2
Premature terminations†	2
Patients finally entering the study	38

*Cataract 1, pre-existing maculopathy 1, mild non-ischaemic CRVO 2.
†Patients who discontinued therapy after two weeks.

During the initial ophthalmological evaluation the following examinations were done: visual acuity (Snellen chart at 6 m, fully refracted), slit lamp examination of the anterior segment, gonioscopy and fundus biomicroscopy (direct and indirect), applanation tonometry, visual fields (Goldmann), colour photography of the fundus, and fluorescein angiography. Fundus fluorescein angiograms were repeated after three and 12 months. The visual acuity test was done weekly during the first three weeks and again, along with all other procedures mentioned, after six weeks and three, six, and 12 months.

To reduce variance all visual acuity determinations were done by two of us (L.L.H. and P.D.), and the fundus was examined by one of us (L.L.H.).

Concerning the fundus biomicroscopy we paid special attention to the extent and character of retinal haemorrhages (deep, superficial, subhyaloid), and oedema. The macula was carefully examined for microcysts, cystoid degeneration, premacular gliosis, and serous detachments or degenerative changes of the pigment epithelium. The number and region of cotton wool spots was recorded. Opticociliary veins and collaterals were noted.

Fluorescein angiograms of the posterior pole were used to evaluate areas of retinal capillary non-perfusion, completeness of the perifocal arcade, leakage from capillaries and main veins, and, in late stages, intraretinal microvascular abnormalities and new vessel formation. Arteriovenous transit time was estimated from the appearance of the dye in the retinal arteries until the complete filling of the major and central retinal veins.

After complete medical and ophthalmological examination each patient was randomly assigned (lottery system) to either a control group (photocoagulation) or a haemodilution group (photocoagulation and haemodilution). Patients were not treated in a blind manner because it is not possible to hide the paleness of a patient with haemodilution from the investigator.

Panretinal photocoagulation (xenon-arc, Zeiss, Oberkochen) was done within two days after admission. After retrobulbar anaesthesia 200 to 250 burns were placed in a scattered manner outside the temporal arcades, and a distance of one or two disc diameters was kept from the papilla. The central burns were 3°, and those placed more peripherally 4·5°, both of 1 s duration.

Haemodilution was induced as described before. On the first day 500 ml of whole blood was taken (Biopack P double plasmaphorese bag, containing 75 ml ACD stabilisator according to *USP* per 500 ml of blood, Biotest-Serum-Institut, Frankfurt/M, FRG) and centrifuged at 3500 rpm for 10 min. Then the plasma was separated (including the buffy coat) and slowly retransfused into the patient. During and after centrifugation approximately 150–250 ml of low molecular weight dextran (MW 40 000) was infused to keep the patient in an almost perfect isovolaemic balance. Possible anaphylactic reactions induced by dextran-reactive IgG antibodies were prevented by intravenous injection of 20 ml of small dextran molecules (MW 1000, Promit, Knoll AG, Ludwigshafen, FRG) once a week.

The same procedure was repeated three to six times within the next 10 days until a haematocrit level of 30–35% was reached. Thereafter, until a period of six weeks' treatment had been reached, haemodilution was done whenever the PCV exceeded 35%. Only during the first 10 days did the patients stay in the hospital.

Statistical variation of the results is expressed as standard deviation of the mean (mean±SD) if not otherwise mentioned. Significance of the differences between corresponding values was tested by the *t* test. Visual acuity changes were tested by Fisher's exact test,[19] based on the χ^2 distribution (2×2 table).

Results

Of 53 patients with either ischaemic or non-ischaemic CRVO referred to our clinic 15 had to be excluded for various reasons (Table 1), so that a total of 38 patients was left. These patients were randomly assigned to either the haemodilution (photocoagulation and isovolaemic haemodilution) or control group (photocoagulation only). Thirty four patients could be followed up for one year, two for six months, and two for only three months.

Table 2 shows the coincidental medical and ophthalmological diseases. The high incidence of atherosclerosis, systemic hypertension, and hyperlipaemia was evident. Only four of 19 patients in each group did not show cardiovascular risk factors. We found one patient with stenosis of the ophthalmic artery as shown by Doppler sonography though there were no signs of carotid occlusive disease. Three patients in the control group and five in the haemodilution group received medical therapy for newly detected congestive heart failure or systemic hypertension. Preexisting cardiac or antihypertensive therapy was maintained. Treatment with pentoxyfylline or acetylsalicyclic acid was discontinued.

Some general medical data and the ophthalmological features of both patient groups at the time of entrance into the study are depicted in Table 3. No significant differences existed between the two groups with respect to age, haematocrit, and duration of occlusion before entering the trial. The same holds true for ophthalmological findings before the start of therapy. Taking into account visual acuity, visual fields, biomicroscopy of the fundus, and fluorescein angiograms,[20-22] 13 patients showed ischaemic CRVO (haemorrhagic retinopathy)—a rather high proportion of about 34%. This might be due to the fact that mild cases of non-ischaemic CRVO are often not referred to our clinic for inpatient treatment.

Table 2 *Medical and coincidental ophthalmological diseases*

Disease	*Photocoagulation, no of patients*	*Photocoagulation and haemodilution, no of patients*
Atherosclerosis vascular diseases*	11	6
Systemic hypertension	8	11
Diabetes mellitus	2	1
Hyperlipaemia	5	4
Supra-aortic artery stenosis	1	0
Glaucoma	3	3
Old retinal vein occlusion of the other eye	1	2

*Angina and/or history of myocardial infarction, cerebrovascular infarction, peripheral arterial occlusive disease.

Table 3 *Entrance data of patients*

	Photocoagulation	*Haemodilution and photocoagulation*
No of patients	19	19
Age (years)	71·3±8·9	67·6±8·5*
Haematocrit (%)	43·4±3·0	44·5±3·8*
Duration of occlusion (days)	36±30	44±35*
Visual acuity:		
≥6/15	7	6
6/20–6/60	7	5
≤6/120	5	8
Visual fields (Goldmann):		
Absolute central scotoma (I4e)	9	10
Peripheral defects (I2e)	13	9
No defects (I2e)	4	2
Biomicroscopy of fundus:		
Cystoid macular oedema	15	15
No of cotton wool spots ≥10	6	7
No of cotton wool spots <10	4	5
Ischaemic CRVO	6	7

*Not significantly different from photocoagulation group.

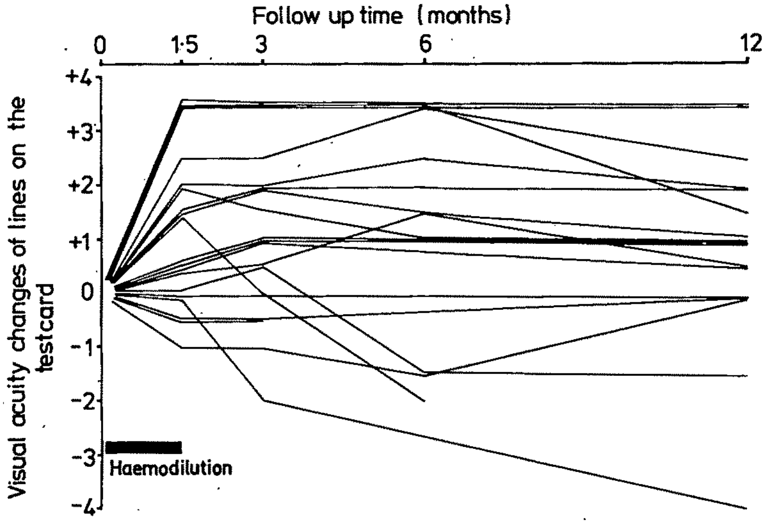

Fig. 1 *Course of VA changes in patients after a haemodilution and photocoagulation. The individual steps of improvement or deterioration are given in Fig. 3.*

Panretinal photocoagulation was quite similar in strength with 222±27 burns in haemodiluted patients and 221±23 burns in controls.

A therapeutic low level of PCV could be maintained for at least six weeks after cessation of haemodilution. In some cases the patient did not reach the pretherapeutic level until after four to five months (Table 4). Isovolaemic haemodilution was a well tolerated therapeutic procedure in most patients. No patient suffered from serious complications. One of the two patients who refused further treatment had a short fainting spell during the third haemodilution that was interpreted as a vagovasal syncope. Two or three of the patients complained of being easily fatigued by physical exertion. Three patients who felt disturbed by restricted physical activity due to dyspnoea were all more than 75 years old. ECG in these patients remained unchanged.

The course of the visual acuity (VA) over the

Table 4 *Haematocrit and thrombocytes of haemodiluted patients*

	No of patients	*Packed cell volume (%)*	*Thrombocytes 1000 cells/ml*
Before treatment	19	44·5±3·8	214±54
6 weeks	19	31·7±2·1*	299±49†
3 months	18	38·4±5·6†	251±59
6 months	10	43·4±3·4	—
12 months	15	42·9±5·1	—

*p<0·01 compared with pretreatment level.
†p<0·05 compared with pretreatment level.

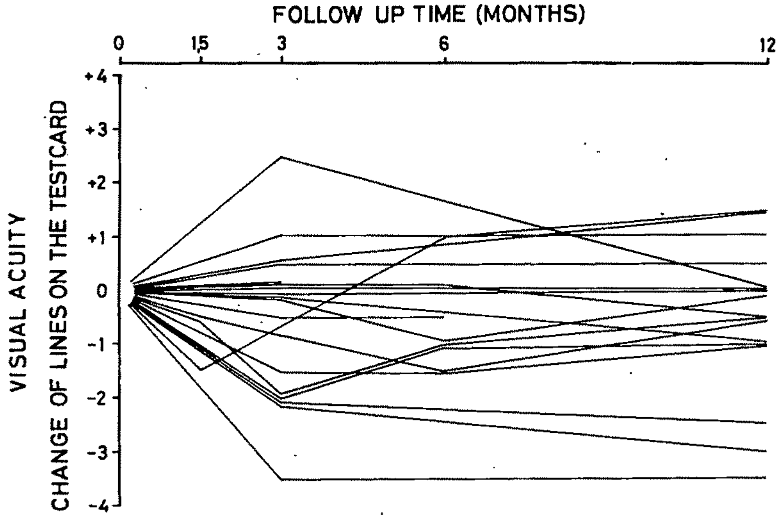

Fig. 2 *Course of VA changes in patients after photocoagulation only. Individual steps of improvement or deterioration are given in Fig. 3.*

whole follow up period is depicted in Figs. 1 and 2. It was obvious that the main increase in VA in the haemodiluted patients occurred during the first six weeks, with only a few patients improving up to three or six months later (Fig. 1). If there is no improvement starting within the first four weeks of haemodilution, no substantial gain in VA can be expected. A true relapse with deterioration of fundus signs, visual fields, and fundus fluorescein angiograms occurred in four patients, in two despite an already low haematocrit level of 35%.

The development of VA in patients treated with photocoagulation only (Fig. 2) was somewhat different from that of haemodiluted patients. More patients suffered from a visual loss during the first three months. However, most of them recovered even after the sixth month, so that the final visual outcome was not significantly different from the initial VA.

VA results three months after commencement of therapy are shown in Fig. 3. This is at the time when, in most haemodiluted patients, a normal haematocrit is reached again, and a rheogenic effect can no longer be expected. A change in visual acuity was considered to be present when the patient could read at least two lines more on the text card. Among the haemodiluted patients seven improved by two to four lines on the Snellen chart; 12 remained unchanged; no patient deteriorated. On the other hand, in the control group only one patient improved, 12 remained unchanged, and five became worse. Statistical analysis by the exact Fisher test for 2×2 tables showed statistical significance ($p<0{\cdot}05$) for the improvement of the haemodiluted patients.

Fig. 4 indicates that one year after starting the therapy there was no fundamental change in the visual outcome compared with the three-month results, though one haemodiluted patient deteriorated by four lines. In five of 17 patients in the haemodilution group visual acuity was still better by two or more lines, whereas none of the control patients had improved ($p<0{\cdot}05$).

In both groups final VA was certainly worse for ischaemic than non-ischaemic CRVO. However, as regards the increase in VA the most marked improvements were reached with haemodilution in patients with ischaemic CRVO, of whom four of six still had better VA one year after treatment. Not one of the six control patients with ischaemic CRVO showed improved VA. This finding had not reached statistical significance, as the numbers of patients were too small for testing, so it should be an important point in further studies on haemodilution.

One year after starting therapy the appearance of

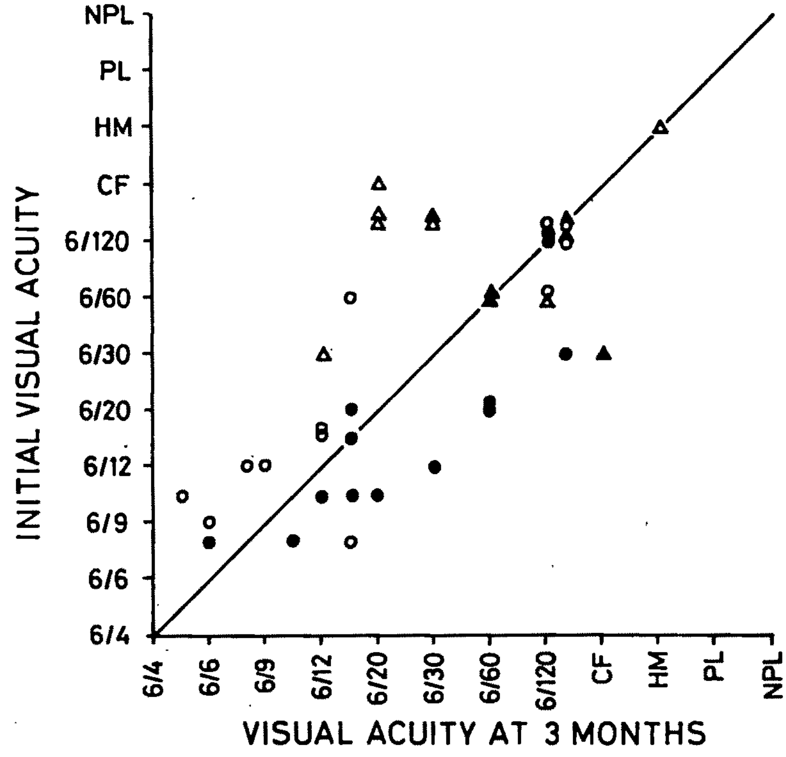

Fig. 3 *Visual acuity before and three months after the start of therapy. Closed symbols mark photocoagulation. Open symbols mean photocoagulation and haemodilution. Circles stand for non-ischaemic CRVO, triangles for ischaemic CRVO.*

Table 5 *Appearance of posterior pole after one year*

	Photocoagulation	*Haemodilution and photo-coagulation*
Total No of patients	17	17
Macular findings:		
Normal	2	2
Minor pigment epithelial changes	1	4
Persistent macular oedema	7	6
Major pigment epithelial changes and/or retinal atrophy	1	2
Macular fibrosis	6	3
Intraretinal microvascular abnormalities (posterior pole)	15	11
Collaterals on disc	8	9
Preretinal vessels	0	0

the retina (Table 5) was quite similar in both groups whether haemodiluted or not. No preretinal vessels could be observed, and no neovascular glaucoma had developed. About half of the patients had collaterals on the disc, but none of them had real neovascularisations as determined by fluorescein angiography. Intraretinal microvascular abnormalities were common, but less so in the haemodilution group.

The macular findings in the two groups did not differ very much. In the haemodilution group there were more patients with minor macular changes and fewer patients with macular fibrosis, which explains why this group had a better overall visual outcome than the control group.

Discussion

Isovolaemic haemodilution was used as a new therapeutic concept to treat patients with CRVO. The general aim was to increase the fluidity of blood. Blood viscosity can easily be decreased by lowering the haematocrit level and replacing the lost circulation cell volume with low molecular weight dextran or other substitutes. Microcirculation, and thus oxygen supply, are improved. Oxygen pressure within the tissue is constant or even higher than normal, until a haematocrit level of some 20–25% is reached. The compensatory increase in cardiac output is mainly achieved by an increased arteriovenous O_2-difference and stroke volume.[23 24]

The rationale for doing such an invasive therapy in patients with CRVO is twofold: (1) Independent of the primary event in CRVO the blood flow decreases in venules and capillaries, leading to vascular leakage and lower shear rates. The resulting increase in local

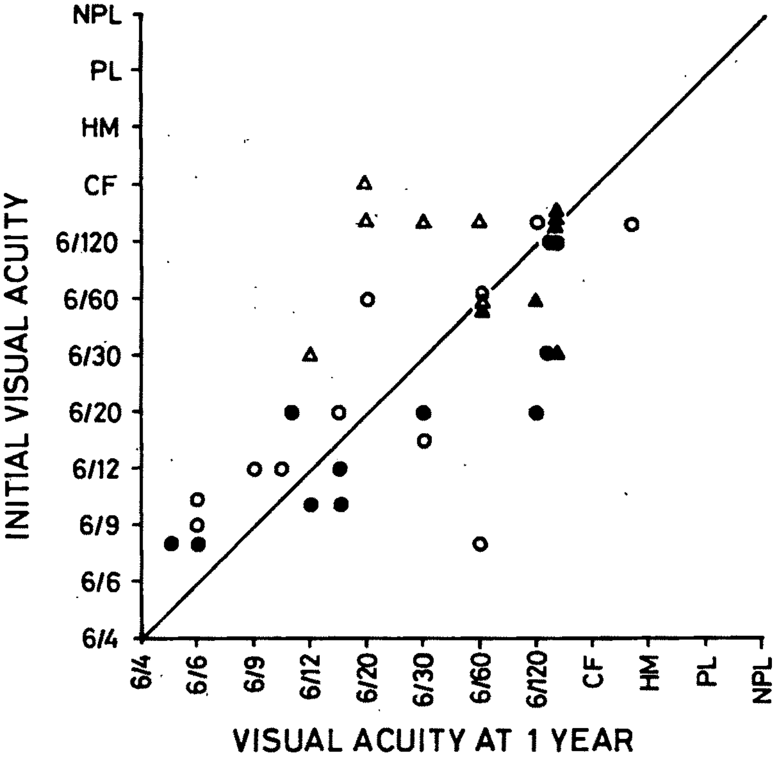

Fig. 4 *Visual acuity before and one year after the start of therapy. Closed symbols mark photocoagulation. Open symbols mean photocoagulation and haemodilution. Circles stand for non-ischaemic CRVO, triangles for ischaemic CRVO.*

blood viscosity certainly strengthens the vicious circle that may ultimately produce progressive ischaemic capillaropathy. (2) In two laboratories patients with CRVO have been shown to have higher than normal whole blood and plasma viscosity values.[12,13] Studies on cerebral and retinal blood flow have reported an increase in blood flow when whole blood viscosity was reduced by haemodilution.[14,15]

Uncontrolled studies of hypervolaemic[25] and isovolaemic haemodilution[17] in 10 patients with CRVO were quite promising. However, haemodilution alone did not prevent neovascular glaucoma. Therefore in the present study panretinal photocoagulation was done in all patients before haemodilution was started. We applied fewer burns compared with Laatikainen *et al.*,[1] but it has been shown by May *et al.*[2] that a total of 120–300 burns prevented neovascular glaucoma. It is questionable whether this is a necessary procedure in all patients with CRVO, because it has been shown that only widespread capillary occlusion leads to rubeosis iridis and/or neovascular glaucoma.[1,2,20,21,26,27] However, some patients who initially present non-ischaemic types of CRVO may later develop ischaemic CRVO. Hayreh[22] noted 7% such patients. In addition, estimates of about 10% to 27% have been made[3,22,28] for those patients who cannot be classified in either group during the first weeks of their presentation. We think that carefully performed panretinal photocoagulation is a relatively safe procedure compared to the risk of neovascularisation in patients with an unknown course of CRVO. The only complication we saw in 38 patients was a transient choroidal effusion in one patient.

There were two methodological drawbacks in our trial. First, it was not possible to do a double-blind study, because 'placebo haemodilution' is not possible. Second, the important determinations of VA could not be done by anyone not involved in the study. This certainly is a disadvantage that could be partly overcome by standardising these examinations (same examiners, same room, daytime).

However, we think that the main point of comparability, well matched general and ophthalmological entrance data, is excellently fulfilled (Tables 2, 3).

Only 8% of our patients with CRVO had to be excluded for medical reasons. Until now the only treatment that seems to be of benefit for the visual outcome is fibrinolytic therapy.[5,6,8] However, fibrinolysis has some important shortcomings that limit its application to relatively young people with a short duration of symptoms. These limitations do not apply for isovolaemic dilution, and one has to take into account that CRVO is predominantly a disease of the elderly.

Visual prognosis of CRVO is strongly dependent on the degree of retinal capillary occlusion. The visual outcome of the ischaemic CRVO is always very poor, whereas the non-ischaemic type often runs a benign course. However, analysis of data in the literature shows a wide range of final visual acuities in the latter form. For example, Hayreh[29] claimed that about 50% of the non-ischaemic cases would end with 6/6 or 6/9 without any therapy. On the other hand Laatikainen *et al.*[1] showed that, in serious forms of non-ischaemic CRVO, only one out of 25 patients had a final VA of more than 6/60. This again stresses the importance of well comparable entrance data in randomised trials of CRVO. In our study haemodiluted patients had a better visual outcome than control patients. The course of visual acuity change (Figs. 1, 2) shows an impressive difference between the two groups, especially during the first six weeks. While the VA of the majority of haemodiluted patients rises above the entrance level, the opposite is true of the controls. A comparison on the basis of a two-line improvement yields statistical significance after three months. Although a few relapses occurred, the visual outcome of haemodiluted patients was still significantly better after one year. This shows that a once achieved visual improvement can be maintained without further haemodilution in most responsive patients. Our results are supported by a preliminary report by Brunner *et al.*[30] Kohner *et al.*[7] found no effects from a haemodilution. However, their patients had obviously been treated for only two or three weeks, and the haematocrit levels had been lowered to only 38–42%. In our experience this is not sufficient to yield an improvement.

Thirteen patients in our study had ischaemic CRVO: seven in the haemodilution group, and six in the control group. These numbers were too small for significant conclusions to be drawn from the courses. It is interesting that five of seven patients responded to haemodilution, of whom only one relapsed (Figs. 3, 4), whereas no control patient with ischaemic CRVO had a better final VA. It seems that a decrease in blood viscosity and an improvement of retinal perfusion are of particular importance in ischaemic CRVO. This finding would support the results of Trope *et al.*,[13] who found increased whole blood and plasma viscosity only in patients with ischaemic central and branch vein occlusion. Future studies must show whether this tendency is statistically significant. If it is haemodilution could be used as a special tool to improve the hitherto very poor visual prognosis of this disease.

Haemodilution reduces, but does not prevent, the serious sequelae on the posterior pole. Persistence of oedema and macular scarring were the main causes of poor vision. In the haemodilution group there were

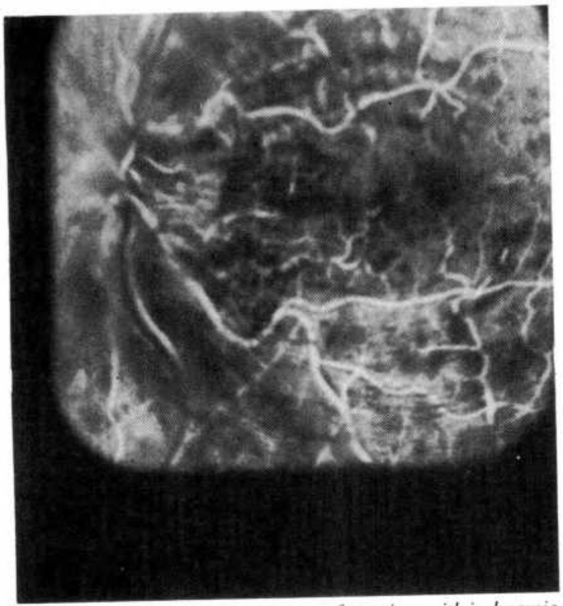

Fig. 5A *Fluorescein angiogram of a patient with ischaemic CRVO. Early arteriovenous phase with strong retinal oedema, haemorrhages, and areas of capillary occlusion before therapy.*

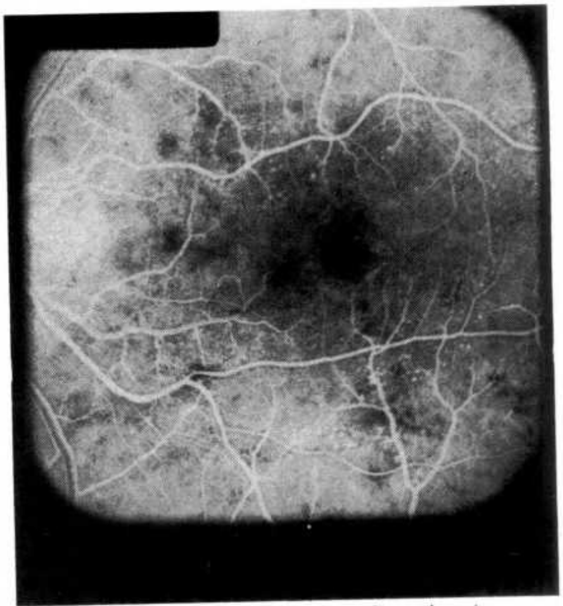

Fig. 5B *Three months after the start of isovolaemic haemodilution the retinal oedema and haemorrhages have profoundly decreased. Intraretinal microvascular abnormalities have developed at the posterior pole, and there is still some leakage of plasma at the foveal arcade. Visual acuity increased from 6/60 to 6/24.*

fewer patients with macular fibrosis and more with only minor foveal changes. The smaller number of patients with intraretinal microvascular abnormalities (Table 5) as seen by fluorescein angiography also points to the beneficial effect of haemodilution (Fig. 5). However, the limited prevention of fundus sequelae and the final visual outcome make it clear that the increase in blood fluidity does not eliminate the cause of CRVO, which is an imbalance between inflow and outflow of blood in the retina. It probably just partially relieves retinal hypoperfusion during a critical time of serious outflow obstruction. We do not know how this outflow obstruction is overcome in some patients. The visible collaterals on the papilla do not characterise patients with better VA, and in our study no difference was found between the two groups (Table 5).

One should expect that the efficacy of higher blood fluidity would be the better the shorter the time lapse between visual disturbance and the start of therapy. Table 6 compares some data of patients with different effects on their VA. Only the occlusion time, that is the duration of symptoms before therapy, is significantly shorter in patients with visual improvement. Age and haematocrit levels do not differ. Nevertheless it has to be mentioned that one patient who had haemodilution on the third day could read only one line more on the test card after one year. Another patient suffering from mild venostasis retinopathy for about four months had an initial VA of 6/9 with mild non-cystoid oedema of the posterior pole. His VA was enhanced to 6/6 under haemodilution, which, however, was not regarded as a significant increase under our conditions. Thus probably milder cases with longstanding macular oedema without cystoid degeneration may be amenable to haemodilution even later than six to eight weeks after first appearance of symptoms.

Isovolaemic haemodilution may constitute a new therapeutic regimen in CRVO. The chance for a better visual outcome is improved, probably mediated by enhanced retinal blood flow[10,16] and prevention of stasis. This method does not eliminate the cause of outflow obstruction and hence has its limita-

Table 6 *Comparison between patients with improved and non-improved VA after haemodilution*

	VA improved	*VA unchanged or decreased*	*Significance*
No of patients	7	12	
Age (years)	65·7±6·9	68·8±9·11	NS
Haematocrit (%)	43·9±4·7	44·9±3·0	NS
Occlusion time:			
Days	25±11	55±40	p<0·01
Range	(10–40)	(3–120)	

tions. Isovolaemic haemodilution is a safe and well tolerated therapy even in elderly patients with signs of cardiovascular disease, when obvious cardiac and respiratory insufficiency have been excluded. If possible, rheological measurements should go beyond the determination of the PCV.[31]

We are grateful to M Helmchen for organising haemodilution of the outpatients; to G Bröskamp and H Kraus for photographic assistance; and to M Koch for preparing the illustrations.

References

1 Laatikainen L, Kohner EM, Khoury D, Blach RK. Panretinal photocoagulation in central retinal vein occlusion: a randomised controlled clinical study. *Br J Ophthalmol* 1977; **61:** 741–53.

2 May DR, Klein MR, Peyman GA, Raichand M. Xenon arc panretinal photocoagulation for central retinal vein occlusion: a randomised prospective study. *Br J Ophthalmol* 1979; **63:** 725–34.

3 Magargal LE, Brown GE, Augsburger JJ, Donoso LA. Efficacy of panretinal photocoagulation in preventing neovascular glaucoma following ischemic central retinal vein occlusion. *Ophthalmology* 1982; **89:** 780–4.

4 Sedney SS. Photocoagulation in retinal vein occlusion. *Doc Ophthalmol* 1976; **40:** 1–226.

5 Kohner EM, Petitt JE, Hamilton AM, Bulpitt CJ, Dollery CT. Streptokinase in central retinal vein occlusion: a controlled clinical trial. *Br Med J* 1976, **i:** 550–3.

6 Weigelin E. Fibrinolysebehandlung bei venösen Verschlüssen der Netzhaut. *Fortschr Ophthalmol* 1982; **79:** 218–22.

7 Kohner EM, Laatikainen LL, Oughton J. The management of central retinal vein occlusion. *Ophthalmology* 1983; **90:** 484–7.

8 Ohrloff C, Trübestein G, Völker B, Weigelin E. Zur Fibrinolyse bei Venenverschlüssen der Retina. *Fortschr Ophthalmol* 1983; **80:** 162–5.

9 Hayreh SS, van Heuven WAJ, Hayreh MS. Experimental retinal vascular occlusion. I. Pathogenesis of central retinal vein occlusion. *Arch Ophthalmol* 1978; **96:** 311–23.

10 McLeod D, Kohner EM. Hemorrhages after central retinal vein occlusion. *Arch Ophthalmol* 1978; **96:** 1921.

11 Retinal vein occlusion (Editorial). *Br J Ophthalmol* 1979; **63:** 375–6.

12 Ring CP, Pearson TC, Sanders MD, Wetherley-Mein G. Viscosity and retinal vein thrombosis. *Br J Ophthalmol* 1976; **60:** 397–410.

13 Trope GE, Lowe GDO, McArdle BM, *et al.* Abnormal blood viscosity and haemostasis in longstanding retinal vein occlusion. *Br J Ophthalmol* 1983; **67:** 137–42.

14 Thomas DJ, Marshall J, Ross-Russell RW, *et al.* Effect of haematocrit on cerebral blood-flow in man. *Lancet* 1977; **ii:** 941–3.

15 Kohner EM, Barnes AB, Hill DW, Young S, Reid AC, Dormandy JH. Effect of viscosity on retinal blood flow. *Proceedings of the 23rd International Congress of Ophthalmology* 1978; 172.

16 Oughton J, Chaine G, Barnes AJ, *et al.* Effect of hemodilution on retinal blood flow. *Clin Hemorheol* 1983; **3:** 234.

17 Wiederholt M, Leonhardt H, Schmid-Schönbein H, Hager H. Die Behandlung von Zentralvenenverschlüssen und Zentralarterienverschlüssen mit isovolämischer Hämodilution. *Klin Monatsbl Augenheilkd* 1980; **177:** 157–64.

18 Hövener G. Lichtkoagulation bei Zentralvenenverschluss. *Klin Monatsbl Augenheilkd* 1978; **173:** 392–401.

19 Fisher RA. *Statistical methods for research workers.* London: Oliver and Boyd, 1950.

20 Hayreh SS. So-called 'central retinal vein occlusion'. I. Pathogenesis, terminology, clinical features. *Ophthalmologica* 1976; **172:** 1–13.

21 Sinclair SH, Gragoudas ES. Prognosis for rubeosis iridis following central retinal vein occlusion. *Br J Ophthalmol* 1979; **63:** 735–43.

22 Hayreh SS. Classification of central retinal vein occlusion. *Ophthalmology* 1983; **90:** 458–74.

23 Messmer K, Sunder-Plassmann L, Klövekorn WP, Holper K. Circulatory significance of hemodilution: rheological changes and limitations. *Adv Microcircul* 1972; **4:** 1–77.

24 Schmid-Schönbein H. Microrheology of erythrocytes, blood viscosity, and the distribution of blood flow in the microcirculation. *Int Rev Physiol* 1976; **9:** 1–62.

25 Radnot M, Follmann P. Rheomacrodex (dextran) in the treatment of the occlusion of the central retinal vein. *Ann Ophthalmol* 1969; **1:** 58–64.

26 Magargal LE, Donoso LA, Sanborn GE. Retinal ischemia and risk of neovascularisation following central retinal vein obstruction. *Ophthalmology* 1982; **89:** 1241–5.

27 Hayreh SS, Rojas P, Podhajsky P, Montague P, Woolson RF. Ocular neovascularisation with retinal vascular occlusion. III. Incidence of ocular neovascularisation with retinal vein occlusion. *Ophthalmology* 1983; **90:** 488–506.

28 Sabates R, Hirose T, McMeel JW. Electroretinography in the prognosis and classification of central retinal vein occlusion. *Arch Ophthalmol* 1983; **101:** 232–5.

29 Hayreh SS. So-called 'Central retinal vein occlusion' II. Venous stasis retinopathy. *Ophthalmologica* 1976; **172:** 14–37.

30 Brunner R, Heinen H, Konen W, Gaethgens P, Hossmann V. Therapy of occlusive disease of retina by pentoxifyllin, isovolemic hemodilution with albumine and hypervolemic hemodilution with dextran. A randomised double-blind study. *Clin Hemorrheol* 1983; **3:** 232.

31 Gallasch G. Neue Ansätze zur Diagnostik und Therapie von Gefäßverschlüssen am Auge. *Fortschr Ophthalmol* 1983; **80:** 166–7.

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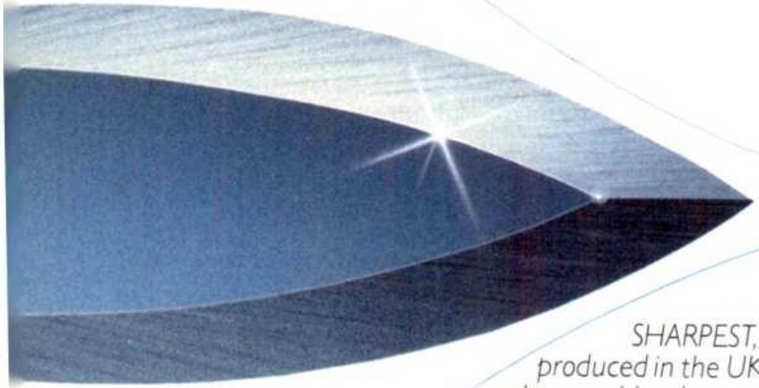

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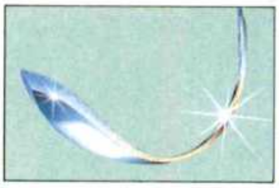

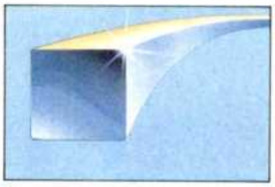

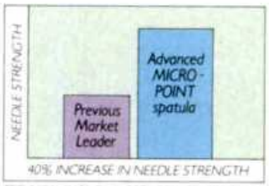

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Ocular hypotensive effect of late pregnancy with and without high blood pressure

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SUMMARY The mean ocular tension of third trimester hypertensive pregnant women did not differ significantly from that of third trimester non-hypertensives, in contrast to the tendency for open-angle glaucoma to be associated with vascular hypertension. Presumably there are different causes for the two types of vascular hypertension. The ocular hypotensive effect of late pregnancy (third trimester) was confirmed.

A significant tendency has been observed for patients with chronic simple glaucoma to have a relatively high blood pressure (compared with non-glaucomatous patients), and for ocular tension to be positively correlated with blood pressure in a group of patients with chronic simple glaucoma and low tension glaucoma.[1] Ocular hypertension is associated with high blood pressure.[2 3]

Ocular tension in pregnancy has been studied occasionally in the past but very seldom in recent years.[4-11] A lower pressure seems to be found consistently in late pregnancy, possibly due to an improved facility of outflow as judged by tonography in the few cases studied.[10 12] No previous study has compared pregnant women with high blood pressure and those without.

Accordingly we have investigated whether the high blood pressure found in late pregnancy might affect the known ocular hypotensive effect of the later months of pregnancy.

Materials and methods

Patients in the first and third trimester of pregnancy were chosen from those attending 'routine antenatal outpatient clinics at the Simpson Memorial Maternity Pavilion. Control patients (25) were obtained in a gynaecological ward. Most (11) were admitted the same morning for minor operations to be done the following day, for example, tubal ligation. Three were ambulatory patients with medical conditions such as salpingitis. Two patients were examined on the day after a 'dilatation and curettage'. None was taking oral contraceptives. The age range of the gynaecological patients was restricted to correspond with that of the pregnant patients. All patients were examined between 1000 and 1230 hours. The eye investigation was done at least 10 minutes after the antenatal examination.

The slightly uneven numbers in the various groups was the result of the availability of patients who agreed to join in the study during its period of about six months.

Eye examination was done for each patient, and included skiascopy and subjective testing. Patients with refractive errors of more than ±1·25 D were excluded, lest the known tendency for high pressure to be associated with myopia and low pressure with hypermetropia might bias the results.[13] This accounted for two exclusions from the control group, one from the first trimester group, three from the third trimester normotensives, and one from the third trimester hypertensives.

Ocular tensions were measured by one observer with a hand-held Perkins applanation tonometer. Brachial blood pressure was measured with a calibrated sphygmomanometer with the patient in the sitting position. The same observer made these measurements. To avoid observer bias on blood pressure, ocular tension was 'frozen' uninspected on the tonometer and left unrecorded until after blood pressure was taken. Inadvertent bias in applanation tonometry is avoided because the end point is assessed while the scale is outside the observer's field of vision, and has to be read subsequently.

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Table 1 *Measurement of ocular tension in three pregnant groups and non-pregnant controls*

Group	*Numbers*	*Median age in years (range)*	*Diastolic BP in mmHg*	*Ocular tension (applanation)* *Mean*	*SD*
(a) Non-pregnant normotensive control	25	27 (19–34)	≤85	14·8*	1·7
(b) First trimester normotensive	20	26 (20–35)	≤85	14·1*	2·6
(c) Third trimester normotensive	33	25 (17–38)	≤85	12·1†	1·7
(d) Third trimester hypertensive	19	28 (21–42)	>85	12·4†	2·2

Groups with mean ocular tensions marked * showed a significant difference from those marked †:
(*a*) vs (c), $t=5·99$, df=56, $p<0·005$.
(*a*) vs (d), $t=3·94$, df=42, $p<0·005$.
(*b*) vs (c), $t=3·07$, df=51, $p<0·005$.
(*b*) vs (d), $t=2·21$, df=37, $p<0·05$.
The difference between each group marked * and each group marked † was not significant. 95% confidence interval for mean difference in ocular tension between normotensives: (*a*) non-pregnant versus (*b*) first trimester is (−0·6, 2·0) and third-trimester: (*c*) normotensive versus (*d*) hypertensive is (−1·5, 0·9).

Randomisation. Only the first tonometrised eyes were included in the analysis, except for a few first eyes excluded by refractive error, in which case second examined eyes were included. Simple randomisation was used to determine for each patient whether the right or left eye was examined first.

Results

Results are presented in Table 1. The mean ocular tension of the non-pregnant normotensive controls did not differ significantly from that of the first trimester normotensive pregnant women, but both were significantly greater than the mean ocular tension of the third trimester normotensives and of the third trimester hypertensives. The very small difference between the mean ocular tension of these last two groups was not significant.

Discussion

The reasons for the relatively low ocular tension found in late pregnancy in both hypertensives and normotensives are speculative but worth detailed consideration. (To prescribe late pregnancy for the treatment of open-angle glaucoma is less facetious than might appear.) Progesterone seems the likeliest effector, as suggested by Becker and Friedenwald,[10] but an effect by relaxin on a background of oestrogen and progesterone is a possibility.[12] Some evidence that systemic administration of progesterone and oestrogen/progesterone combinations causes a fall in ocular tension has been recorded,[10 12 14-16] although controversy exists.[17 18]

Some of progesterone's pharmacological properties might be steroid related with steroid blockade as a possible explanation. Accordingly we made a preliminary trial of progesterone eye drops in three patients. The results have been negative, but that does not invalidate the suggestion that peripheral steroid blockade might be a mechanism of action of progesterone on ocular tension—if indeed that is the relevant active principle of late pregnancy. Recent observations,[19] however, have shown evidence of the ocular hypotensive effect on normal rabbits of eye drops containing a steroid blocker.

A possible fallacy exists in the claim for an ocular hypotensive effect of late pregnancy. It could be that the physiological softening of ligaments in late pregnancy might extend to that of the corneoscleral envelope to produce reduced corneoscleral rigidity and therefore only an apparent fall in intraocular pressure. (However, evidence has been presented previously to support the view that the concept of (corneo-) scleral rigidity should be largely, if not completely, replaced by variations in ocular volume or, more accurately, variations in surface area of the corneoscleral envelope.[20]) Alternatively, improved uveoscleral outflow, which results from the hormonal changes of late pregnancy, is a more likely explanation for a true fall in pressure.

A comment has been made[11] that the relative ocular hypotension in late pregnancy is probably not due to reduced episcleral venous pressure.

Our finding of very similar ocular tension in hypertensive and non-hypertensive groups of third trimester pregnant women contrasts with the association between vascular hypertension and open-angle glaucoma in elderly patients found in a previous study.[1] The discrepancy is probably due to the presumed difference in aetiology between the two hypertensions, but difference in age may be important. Many other possible explanations exist.

A study of non-pregnant non-hypertensives and a cohort of pregnant women followed up from the first trimester would have been a better theoretical protocol than the present cross-sectional one. It was not adopted mainly because of the impossibility of being able to predict what proportion of the pregnant women would have developed hypertension in the last trimester.

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References

1 Leighton DA, Phillips CI. Systemic blood pressure in open angle and low tension glaucoma and normals. *Br J Ophthalmol* 1972; **56:** 447–53.

2 Kahn HA, Leibowitz HM, Ganley JP, *et al.* The Framingham eye study. II. Association of ophthalmic pathology with single variable previously measured in the Framingham heart study. *Am J Epidemiol* 1977; **106:** 33–42.

3 Leske MC, Podgor MJ. Intraocular pressure, cardiovascular risk variables and visual field defects. *Am J Epidemiol* 1983; **118:** 280–7.

4 Imri J. The influence of the endocrine system on intraocular tension. *Endocrinology* 1922; **6:** 213–7.

5 Marx E. L'influence de la menstruation et de la grossesse sur la tension oculaire. *Ann Oculist (Paris)* 1923; **160:** 873–82.

6 Rizzo A. La tensione oculare nella grairindanza. *Zentralbl Gesamte Ophthalmol* 1926; **15:** 864–5.

7 Gurvic B. Sur Frage über Zusammenhang der physiologischen Hyperfuntion der Hypophyse bei Schwangeren mit dem Intraoculardruck. *Zentralbl Gesamte Ophthalmol* 1930; **23:** 19–20.

8 Patal P. Bezienhungen zwischen Augendruck und Schwangerschaft auf grund neuere Untersuchungen. *Zentralbl Gynaekol* 1938; **62:** 868–72.

9 Dominguez WN. Oftalmotono en obsletricia y ginecologia. Un nuevo sigiro para el diagnostico de gestacion. *Sem Med Española* 1951; **98:** 572–7.

10 Becker B, Friedenwald JS. Clinical aqueous outflow *Arch Ophthalmol* 1953; **50:** 557–71.

11 Hørwen I, Gjønnaess H. Corneal indentation pulse and intraocular pressure in pregnancy. *Arch Ophthalmol* 1974; **91:** 92–8.

12 Patteson G, Miller SJH. Hormonal influence in simple glaucoma: a preliminary report. *Br J Ophthalmol* 1963; **47:** 129–37.

13 Tomlinson A, Phillips CI. Applanation tonometry and axial length. *Br J Ophthalmol* 1970; **54:** 548–53.

14 Posthumus R. Use and possibilities of progesterone in the treatment of glaucoma. *Ophthalmologica* 1952; **124:** 17–25.

15 Meyer EJ, Leibowitz H, Christman EH, Niffenegger JA. Influence of norethynodrel with mestranol on intraocular pressure in glaucoma. *Arch Ophthalmol* 1965; **75:** 157–61.

16 Obal A. Gelbkörperhormon—Anwendung zur Glaukomtherapie. *Klin Monatsbl Augenheilkd* 1950; **117:** 201–3.

17 Treumer K. Glaukonbehandlung durch Gelfkörperhormon. *Klin Monatsbl Augenheilkd* 1952; **120:** 523–34.

18 Leydhecker W. *Glaukom, ein Handbuch.* Berlin: Springer, 1960: 444–6.

19 Phillips CI, Green KC, Gore SM, Cullen PM. Eye drops of RU 486-6, a peripheral steroid blocker, lower intraocular pressure in rabbits. *Lancet* in press.

20 Phillips CI, Shaw TL. Model analysis of impression tonometry and tonography. *Exp Eye Res* 1970; **10:** 161–82.

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Efficacy in anterior uveitis of two known steroids and topical tolmetin

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SUMMARY We have compared the anti-inflammatory efficacy of 5% tolmetin sodium dihydrate, 0·5% prednisolone disodium phosphate, and 0·1% betamethasone disodium phosphate in 71 consecutive patients presenting with acute endogenous non-granulomatous uveitis randomly assigned to one of these treatment groups. Inflammatory symptoms and signs were scored during the course of the 21-day trial period. There was no statistically significant difference in the effect on the signs or symptoms of the three drugs tested. 90% of the Betnesol (betamethasone sodium phosphate, benzalkonium chloride) treated group were clinically judged cured compared with 68% of the Predsol (prednisolone sodium phosphate, benzalkonium chloride) treated group, and 57% of the tolmetin treated group.

Endogenous anterior uveitis is an iridocyclitic inflammatory disease of unknown origin. The condition is frequently recurrent and self limiting but requires treatment with non-specific agents such as corticosteroid preparations to suppress the signs and symptoms of inflammation, and mydriatic/cycloplegic therapy to avoid complications associated with inflammatory events in the anterior chamber. In acute endogenous anterior uveitis good control of inflammation is usually achieved with topical corticosteroids. Periocular and/or systemic steroid therapy is rarely required.[1] The beneficial effects of topical corticosteroids in inflammatory eye disease have been fairly well established in recent years. Well controlled double-blind trials have confirmed their efficacy against either standard treatments or placebos in both postsurgical inflammation[2–4] and anterior uveitis.[5–8]

The widespread use of topical corticosteroids is not without clinical problems, however, and these are generally well known. Probably the most significant side effect occurs in the so called steroid responder, where serious and potentially sight threatening increases in intraocular pressure may occur,[9 10] and perhaps the most important contraindication is in ocular inflammation associated with an infectious agent, particularly where that agent is a virus.[11]

There is increasing evidence that prostaglandins are important mediators of the inflammatory process in the eye as well as in other tissues. They have been clearly implicated in postsurgical inflammation and anterior uveitis and may be responsible for many of the clinical features observed in these conditions.[12–14] With this realisation of the important role that prostaglandins play has come an interest in the use of non-steroidal anti-inflammatory agents as potential alternatives to the long established steroid therapy. One such non-steroidal anti-inflammatory drug that has had widespread usage as a systemic treatment for rheumatoid arthritis and allied conditions is tolmetin[15] (Tolectin). This compound, which is a pyrrole acetic acid derivative without the indole nucleus present in indomethacin, is a potent inhibitor of prostaglandin synthetase[16] and has been developed as an ophthalmic solution. Tolmetin is highly effective as a topical anti-inflammatory agent in an experimental model of immunogenic uveitis.[17] Tolmetin ophthalmic solution has also been shown to be beneficial, when compared with saline, in a small group of patients treated after cataract surgery (R Mapstone, personal communication).

The objective of this double-masked trial in patients with acute endogenous non-granulomatous anterior uveitis was to compare the anti-inflammatory efficacy of 5·0% tolmetin ophthalmic solution with two commonly prescribed steroidal preparations, Predsol 0·5% and Betnesol 0·1%.

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Table 1 *Assessments of symptoms and signs of inflammation made on days 1, 3, 7, 14, and 21 of the trial*

Symptom	*Score*
Photophobia	0, 1, 2, or 3
Pain	0, 1, 2, or 3
Blurring	0, 1, 2, or 3
Watering	0, 1, 2, or 3
Sign	
Corneal oedema	0, 1, or 2
Posterior synechia	0, 1, or 2
Ciliary injection	0, 1, 2, or 3
Keratic precipitates	0, 1, 2, or 3
Aqueous flare	0, 1, 2, or 3
Aqueous cells	0, 1, 2, or 3
Vitreous cells	0, 1, 2, or 3
Exudate	0 (absent) or 3 (present)
Hypopyon	0 (absent) or 3 (present)
Ptosis	0 (absent) or 3 (present)
Mobility of aqueous cells (if present)	0 (mobile) or 3 (stationary)

0=None. 1=Mild. 2=Moderate. 3=Severe.

Materials and methods

Patients and trial design. Seventy-one consecutive patients presenting at the Casualty Department of the Manchester Royal Eye Hospital with acute endogenous non-granulomatous anterior uveitis were included in the study. Patients on topical or systemic steroids for other conditions and pregnant women were excluded. The purpose of the trial was explained to each patient, and their verbal consent was obtained. One patient declined to take part in the study.

For each patient a clinical history was taken, and a record form was completed. Details of the patient's subjective assessment of the discomfort of the affected eye, a full detailed slit lamp biomicroscope examination, visual acuities, and intraocular pressure were recorded on the patient's record form. In addition all patients had chest and sacroiliac joint *x*-rays taken.

Patients were assigned consecutive trial numbers (1–71) and thereby allocated to one of three treatment groups by the Pharmacy Department, which held the randomised treatment code. Neither patient nor ophthalmologist was advised of the nature of the treatment. The patients received either tolmetin sodium dihydrate 5·0% solution, prednisolone disodium phosphate 0·5% (Predsol), or betamethasone disodium phosphate 0·1% (Betnesol). They were asked to instil one drop into the affected eye every two hours during the waking period of each day, and this treatment regimen was subsequently reduced by the examining ophthalmologist as required. Initially all patients also received atropine 1·0% once daily.

Assessments. On admission to the trial at the first visit (day 1) a detailed clinical history was taken and record admission forms completed. The patient's symptoms, clinical signs, and intraocular pressure were recorded on day 1 and then on days 3, 7, 14, and 21 of treatment. The symptoms and signs weighted scoring procedure is shown in Table 1. Side effects noted were recorded on days 3, 7, 14, and 21.

Statistical analysis. Much of the data collected were subjective scores, and consequently mainly non-parametric methods have been used for the statistical analyses. These were the Kruskal-Wallis analysis of variance (ANOVA) and the χ^2 tests used to test comparability of treatment groups at the start of the trial and to make comparisons between treatment groups during treatment. The Wilcoxon signed rank test was used for comparisons within treatment groups. Within-group comparisons with baseline scores quote single tail probabilities. Between-group comparisons quote two tailed probabilities. $p<0{\cdot}05$ is considered to be statistically significant.

Results

Patient comparability. Of the 71 patients included in the study on day 1, 11 have not been included in the statistical analyses. Four of the excluded patients did not return to the clinic for follow-up visits at an early stage in the trial. Another four did not reattend at all.

Table 2 *Numbers of cases with mild or severe uveitis at presentation and associations with clinical history data*

Data from clinical history which show factors possibly associated with uveitis and clinical outcome	*Group*					
	Tolmetin		*Predsol*		*Betnesol*	
	Mild	*Severe*	*Mild*	*Severe*	*Mild*	*Severe*
Cases at initial assessment	7	14	8	11	10	10
Cases with clinical or radiological evidence of ankylosing spondylitis or sacroillitis	2	4	3	3	4	3
Cases subsequently withdrawn also with ankylosing spondylitis or sacroillitis	1	4	2	0	1	0
Cases with recurrent or previous uveitis	3	3	4	3	6	6
Cases with ankylosing spondylitis or sacroillitis and previous uveitis	1	0	2	1	4	2

Table 3 *Treatment group mean total scores for patient symptoms at initial visit and at days 3, 7, 14, and 21 during treatment. Statistical significance of within group score reductions assessed by Wilcoxon signed ranks test (one tailed)*

Visit	*Treatment group (number of patients)*								
	Tolmetin (21)			*Predsol (19)*			*Betnesol (20)*		
	Mean score	*% Initial score*	*p*	*Mean score*	*% Initial score*	*p*	*Mean score*	*% Initial score*	*p*
Initial	5·80	100		5·16	100		4·70	100	
3 Days	4·75	82	<0·05	4·42	86	<0·04	2·90	62	<0·003
7 Days	3·85	66	<0·02	3·74	72	<0·005	2·85	61	<0·007
14 Days	3·80	66	<0·006	3·21	62	<0·003	2·45	52	<0·001
21 Days	3·85	66	<0·007	3·00	58	<0·003	2·20	47	<0·001

One patient in the Predsol group was inadvertently changed to treatment with Betnesol, and these results were excluded. Two patients in the Betnesol group developed bilateral uveitis and were removed from the study.

The remaining 60 patients were randomly assigned to groups treated with either topical tolmetin (21 patients), or Predsol (19 patients), or Betnesol (20 patients). Patient comparability assessed on the initial visit was good. There were no significant differences between the groups. The mean age was 40–45 years (range 13–72 years), and the proportion of females to males (approximately 2:1) was similar in all groups. There were no significant differences in the number of previous attacks. Over one-third of the patients had had no previous attack of uveitis. The duration of present symptoms was also similar in all three groups. Approximately 40% of patients had had their present attack symptoms for more than three days and over 80% of patients for more than seven days.

Analysis of records of past medical and family history was carried out, but nothing was found to suggest that the randomised treatment allocation of patients to treatment groups resulted in dissimilar groups. The results are shown in Table 2.

Statistical analysis. During the course of the trial a number of patients were removed from the study because of lack of response to treatment. Where this occurred the last available signs and symptoms scores have been carried over into missing assessment periods until the end of the trial (21 days). This procedure introduces less bias into the analysis than some alternative procedures, such as our ignoring all results relating to such patients.

Symptom scores. The patients' symptoms were assessed by our questioning the patient according to the scoring scheme shown in Table 1 at the initial visit and subsequently at 3, 7, 14, and 21 days.

The four symptom scores were summed for each patient and mean total symptom scores determined for each group. Statistically significant improvements in total symptom scores were seen in all three treatment groups at days 3, 7, 14, and 21. These data are shown in Table 3 and Fig. 1. Between-group comparisons showed no statistically significant difference

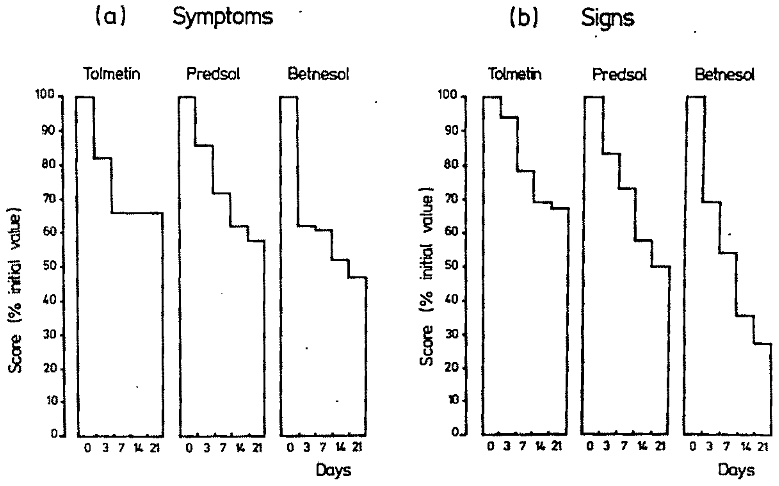

Fig. 1 *Change in symptom and sign scores after treatment with tolmetin, predsol, or betnesol as a percentage of initial score.*

Table 4 *Treatment group mean total scores for patient signs of inflammation at initial visit and at days 3, 7, 14, and 21 during treatment. Statistical significance of within group score reductions assessed by Wilcoxon signed rank test (one tailed)*

Visit	*Treatment group (number of patients)*								
	Tolmetin (21)			*Predsol (19)*			*Betnesol (20)*		
	Mean score	*% Initial score*	*p*	*Mean score*	*% Initial score*	*p*	*Mean score*	*% Initial score*	*p*
Initial	9·65	100		9·10	100		7·50	100	
3 Days	9·05	94	<0·05	7·53	83	<0·006	5·20	69	<0·001
7 Days	7·50	78	<0·03	6·63	73	<0·032	4·05	54	<0·001
14 Days	6·70	69	<0·03	5·21	57	<0·011	2·70	36	<0·001
21 Days	6·50	67	<0·02	4·58	50	<0·010	2·10	28	<0·001

in either total symptom scores at 1, 3, 7, 14, and 21 days or change in total symptom scores at days 3, 7, 14, and 21.

Sign scores. Signs were assessed by the examining ophthalmologist according to the scheme shown in Table 1 at the initial visit and subsequently at 3, 7, 14, and 21 days.

Because individual sign scores are weighted for severity of the sign, it is permissible to sum the scores for each patient in order to obtain an overall total sign score that represents a measure of inflammation for that patient. This is a statistical procedure used in previous trials of this sort.[6,7] Table 4 and Fig. 1 show treatment group mean total sign scores at the initial visit and at subsequent follow-up, together with a within-group statistical analysis. Comparisons between treatment groups for either total sign scores at days 1, 3, 7, 14, and 21 or change from baseline total sign scores at days 3, 7, 14, and 21 showed no statistically significant differences between the three groups. Nevertheless the trend shows that the greatest and most rapid response was seen in the Betnesol treated group. Predsol and tolmetin gave similar results.

Stratified formal analysis. An alternative approach to the analysis of the three groups would have been to stratify the patients into mild or severe cases based on the absence or presence of certain signs.[6] It was felt that more reliance could be placed on ocular sign scores than the subjective symptom scores. Patients were classed as severe if, at their initial assessment, they had any of the following signs: ptosis, exudate, stationary aqueous, or hypopyon.[6] The results of this analysis are shown in Table 5. The Predsol and Betnesol treated groups had a similar distribution of mild and severe patients, but the tolmetin group had twice as many cases in the severe category as in the mild category.

At the end of the trial patients were classified by one of us (JAD) as cured or not cured on a clinical impression basis. The results of this analysis are also shown in Table 5. Cure rates were similar for tolmetin and Predsol but better for Betnesol.

Intraocular pressure. Intraocular pressure (IOP) was measured in most patients in both the inflamed and non-inflamed eyes. IOP was often lower in the affected eye at the initial visit. In 17% of patients pressures were the same and in 25% higher than in the non-inflamed eye. The distribution was similar in all three groups. In 40–50% of the patients the pressure rose slightly during the trial and remained the same or decreased in the remainder. Only one patient showed a large rise in IOP at any time during the trial (at day three in the Predsol group), but the pressure returned to near normal by the end of the trial.

Side effects. Six out of 20 patients (30%) in the tolmetin group commented on transient stinging of the eye with the tolmetin drops. One patient in the Predsol group complained of eye irritation with the Predsol drops, and two patients in this group complained of stinging of the eye with atropine. There were no complaints of stinging or irritation in the Betnesol group.

Table 5 *Clinical judgment of treatment success or failure*

Group	*Number cured/ number at start*	*Cured %*	*Initial assessment of cases*		*Assessment of cases cured*	
			Mild	*Severe*	*Mild*	*Severe*
Tolmetin	12/21	57	7	14	5	7
Predsol	13/19	68	8	11	3	10
Betnesol	18/20	90	10	10	9	9

Discussion

This trial has shown that as regards patient symptoms there was little difference between the three treatment groups, which confirms previous studies[6,7] showing that this improvement is brought about by atropine or the natural behaviour of the disease. When we compared reductions in inflammatory signs Betnesol was found to be superior to Predsol and tolmetin, but the power of the trial was such that this difference did not reach statistical significance. As shown in the stratified formal analysis it is evident that the trial was weighted against tolmetin, because that particular group had the highest number of severe cases at the outset of the trial.

As previous trials have shown,[6,7] most cases of mild uveitis would probably resolve without the use of anti-inflammatory agents, and one is therefore most concerned about the treatment of severe cases. The difficulty arises, however, when cases are initially assessed. There is no way of knowing, on clinical grounds, which cases will remain mild or moderately affected and which cases will become severe, and so all cases must be treated.

An indication of the variable course of the disease can be seen in an analysis of the cases withdrawn or failed. Of six cases failed in the Predsol group five were mild initially, and of nine cases withdrawn in the tolmetin group seven were severe initially. Of the 12 cases successfully treated in the tolmetin group seven were severe initially. If a stratified trial is to be used, then very large numbers of cases are required to be able to carry out within- and between-group analyses of sufficient power. In this trial the numbers were too low to allow any reasonable comparisons after stratification.

It would be extremely helpful if there were some factors present that might indicate whether a particular case would be severe and therefore definitely require anti-inflammatory treatment. A previous study[18] has shown a high percentage of HLA-27 positive antigen in severe cases and in patients with a previous history of uveitis, and shows its close aetiological relationship to ankylosing spondylitis and Reiter's syndrome. HLA studies, however, are expensive and not usually routinely done on uveitis cases. In the present trial there was a fairly even spread of cases with previous uveitis or clinical or radiological evidence of ankylosing spondylitis or sacroiliitis between the mild and severe groups. Therefore, there are no factors here that would indicate those cases likely to be severe.

Non-steroidal anti-inflammatory agents may not prove to be completely effective in acute endogenous non-granulomatous uveitis, because the lymphocytic infiltrations associated with this condition are probably modulated by products of arachidonic acid metabolism other than the ubiquitous prostaglandins. Further clinical trials of tolmetin in other models of inflammation such as postoperative and traumatic uveitis, where prostaglandins play a more major role in the inflammatory condition, are clearly indicated before topical tolmetin can be unequivocally recommended, but the results of this trial certainly warrant such studies.

Tolmetin will have a clinical advantage over steroidal preparations only if it can be shown that it does not have their disadvantages. Non-steroidal anti-inflammatory agents are effective in both normal and adrenalectomised animals, and widespread clinical usage has shown that adrenal suppression does not occur. Unlike the steroids there is no evidence that topical tolmetin has any adverse effect on intraocular pressure.[19] Five known steroid responders treated with 5·0% tolmetin three times a day for six weeks showed no ocular pressure rise (R Mapstone, personal communication). In a murine model of viral keratitis, in which topical steroids are known to enhance viral replication, topical tolmetin did not do so and was indistinguishable from saline in this regard (A B Tullo, personal communication).

Young *et al.*[20] reported that they could detect no statistically significant differences between Predsol, saline, and tolmetin in a trial similar to our own. Trials have been carried out with placebo controls and positive (steroid) controls in which differences were observed with their use in anterior uveitis, as mentioned earlier, and so it is difficult to draw conclusions from their study. We did not include a placebo control group and are therefore unable to make unequivocal statements about the true efficacy of either of the steroids we tested or of tolmetin. It is possible to say only that tolmetin was statistically indistinguishable from either Predsol or Betnesol, and that further clinical trials are indicated.

We are most grateful to all the consultants at Manchester Royal Eye Hospital for referring their patients to us. The tolmetin eyedrops were provided by Smith and Nephew Research Ltd, and this paper would not have been possible without the expert statistical analyses carried out by Mrs K. Shawley. We are also most grateful to Mrs Joyce Marlow for secretarial assistance.

References

1 Luntz MH. A clinical approach to the medical treatment of uveitis. *Adv Ophthalmol* 1978; **36:** 187–96.
2 Knopf MM. A double blind study of fluoromethalone. *Am J Ophthalmol* 1970; **70:** 739–40.
3 Fairbairn WD, Thorson JC. Fluorometholone. Anti-inflammatory and intra-ocular pressure effects. *Arch Ophthalmol* 1971; **86:** 138–41.
4 Corboy JM. Corticosteroid therapy for the reduction of postoperative inflammation after cataract extraction. *Am J Ophthalmol* 1978; **82:** 923–7.
5 Hunter PJL, Fowler PD, Wilkinson P. Treatment of anterior

uveitis. Comparison of oral oxyphenbutazone and topical steroids. *Br J Ophthalmol* 1973; **57:** 892–6.

6 Dunne JA, Travers JP. A double-blind clinical trial of topical steroids in anterior uveitis. *Br J Ophthalmol* 1979; **63:** 762–7.

7 Ramsell TG, Bartholomew RS, Walker SR. Clinical evaluation of clobetasone butyrate: a comparative study of its effects on postoperative inflammation and on intraocular pressure. *Br J Ophthalmol* 1980; **64:** 43–5.

8 Eilon LA, Walker SR. Clinical evaluation of clobetasone butyrate eyedrops in the treatment of anterior uveitis and its effect on intraocular pressure. *Br J Ophthalmol* 1981; **65:** 644–7.

9 Goldman H. Cortisone glaucoma. *Arch Ophthalmol* 1962; **68:** 621.

10 Becker B, Mills DW. Corticosteroids and intra-ocular pressure. *Arch Ophthalmol* 1963; **70:** 500.

11 Patterson A, Jones BR. The management of ocular herpes. *Trans Ophthalmol Soc UK* 1967; **87:** 59.

12 Whitelocke RAF, Eakins KE, Bennett A. Acute anterior uveitis and prostaglandins. *Proc R Soc Med* 1973; **66:** 429–34.

13 Podos SM. Prostaglandins, non-steroidal anti-inflammatory agents and eye disease. *Trans Am Ophthalmol Soc* 1976; **74:** 637–60.

14 Mishima S, Masuda K. Prostaglandins and the eye: a review of clinical implications. *Metab Pediatr Ophthalmol* 1979; **3:** 179–86.

15 Brodgen RN, Heel RC, Speight TM, Avery G. Tolmetin: a review of its pharmacological properties and therapeutic efficacy in rheumatic diseases. *Drugs* 1978; **15:** 429–50.

16 Taylor RJ, Salata JJ. Inhibition of prostaglandin synthetase by tolmetin (Tolectin McN-2559), a new non-steroidal anti-inflammatory agent. *Biochem Pharmacol* 1976; **25:** 2479–84.

17 Gilbert D, Horlington M. Effects of a topically applied non-steroidal anti-inflammatory drug, tolmetin, on experimentally induced uveitis in the rabbit. *Proc Int Soc Eye Res* 1982; **2:** 105.

18 Mapstone R, Woodrow JC. HL-A 27 and acute anterior uveitis. *Br J Ophthalmol* 1975; **59:** 270–5.

19 Gilbert D, Kolthammer J, Wigens A. Effects of a topically applied non-steroidal anti-inflammatory drug, tolmetin, on the intra-ocular pressure of normal rabbits and of human steroid responders. *Proc Int Soc Eye Res* 1982; **2:** 107.

20 Young BJ, Cunningham WF, Akingbehin T. Double-masked controlled clinical trial of 5% tolmetin versus 0·5% predinsolone versus 0·9% saline in acute endogenous non-granulomatous anterior uveitis. *Br J Ophthalmol* 1982; **66:** 389–91.

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Studies on retinitis pigmentosa in man.
II. Erythrocyte osmotic fragility

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SUMMARY The osmotic fragility of erythrocytes from patients with genetically classified forms of retinitis pigmentosa (RP) has been studied. The mean fragility was increased in autosomal dominantly inherited RP, where the dystrophy was expressed regionally in the retina, with both rods and cones affected. In contrast it was normal in patients with the dominantly inherited disease, which leads to a diffusely distributed dystrophy of, predominantly, rod photoreceptor cells. Raised osmotic fragility of erythrocytes has also been observed in female patients with multiplex (recessive) RP and in female carriers of the X-linked form of the disease.

Retinitis pigmentosa (RP) is the name given to a group of inherited diseases, generally of unknown aetiology, which lead to the degeneration of rod photoreceptor cells; cones may also be affected. In our studies on RP in man we have adopted the premise that there might be a generalised metabolic lesion that is expressed overtly in photoreceptors because of their unique composition, function, and/or environment.[1]

The response of erythrocytes to hypotonic insult provides a simple monitor of general body homoeostasis, since it is influenced not only by the metabolic status of the cells but also by the composition of plasma.[2] We have therefore routinely included the test in our studies on patients with RP, and here we report our initial findings. Erythrocyte osmotic fragility varies with the age of the donor and the turnover time of the cell population.[3-5] The latter is reflected in heterogeneity of cell fragilities within individual samples.[6] In the course of the study we also detected sex-related differences.[5] We have therefore considered these variables in the evaluation of our results.

Several distinct inheritance patterns of RP are recognised. They include autosomal dominant, X-chromosome-linked (X-hemizygote), and autosomal recessive. The last is most clearly distinguished when brothers and sisters express the disease but there is no other affected relative, a category referred to by Jay[7] as mixed multiplex. As in our previous study,[8] we have used this terminology, referring also to RP patients with no known affected relative as simplex.

Materials and methods

The patients reported on here attended the Genetic and Electrodiagnostic Clinics of Moorfields Eye Hospital, London, where the category of retinal dystrophy was defined genetically, clinically, and where possible by psychophysical and electrophysiological tests.[9-11] In particular, patients with autosomal dominantly inherited disease were divided into those with a diffuse loss of, principally, rod vision (D type), and those with more regionalised retinal lesions and significantly affected cone as well as rod vision (R type) (Ernst WJK, Lyness AL, personal communication).

Osmotic fragility was determined with hypotonic, phosphate-buffered saline, pH 7·4, as described by Dacie and Lewis.[12] Heparinized blood (50 µl) was mixed with 5·0 ml buffered saline (12 tubes with dilutions ranging from 1·0 to 9·0 g/l NaCl), and after 30 min at room temperature the absorbance at 540 nm of the centrifuged solutions was measured.

Haemolysis curves were constructed from the experimental data, and a linearising transform[3] was applied to permit linear regression statistics to characterise the osmotic fragility curve by its mean cellular fragility, X-50 (that is, the molar NaCl concentration at 50% haemolysis) and the fragilities distribution parameter, β. A broadening of the range of fragilities would be quantified with a decrease in β. Results are expressed as the mean±SEM.

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Table 1 *Osmotic fragility of erythrocytes from patients with retinitis pigmentosa*

Category	*Males*			*Females*		
	Number	*Age*	$X-50\times10^3$†	*Number*	*Age*	$X-50\times10^3$†
(1) 'Normal'	36	40±2	73·5±0·4	42	47±3	72·0±0·4
(2) Autosomal dominant (R type)	6	46±6	76·0±0·9*	11	43±5	75·3±0·8***
(3) Autosomal dominant (D type)	5	26±2*	71·0±1·6	8	37±4	72·2±0·5
(4) X-linked hemizygote	16	33±3	72·1±0·7			
(5) X-linked heterozygote				13	36±4	73·6±0·5*
(6) Multiplex	6	46±6	74·6±0·3	5	51±6	74·5±0·6**
(7) Simplex	11	40±4	73·4±0·7	5	40±10	72·8±0·8

*$p<0{\cdot}05$, **$p<0{\cdot}02$, ***$p<0{\cdot}001$ when compared with the normal group.
†Results expressed as moles/litre NaCl: see text for explanation.
Categories: (1) Apparently healthy volunteers. (2) Males and/or females affected in more than one generation: regionalised retinal lesions. (3) As (2) but diffuse retinal lesions. (4) X-chromosome-linked RP: affected males. (5) Female 'carriers' of (4). (6) Siblings express the disease; no other known affected relative. (7) No known relative with the disease.

Results and discussion

The mean osmotic fragilities of erythrocytes obtained from patients with retinitis pigmentosa are shown in Table 1. The most striking result is the raised fragility of cells from patients with the dominantly inherited disease that leads to regionalised lesions and to the degeneration of both rod and cone photoreceptors. β Values did not significantly differ from normal (control males, 323±10, n=36; R type, 265±28, n=6; control females, 317±8, n=42; R type, 301±21, n=11). This suggests that erythrocyte turnover was not impaired and that the change is caused not by age variation in the cell population but by metabolic or extracellular factors—for example, plasma composition. The result is made more intriguing because of the normal fragility seen in the group of patients who also had autosomal dominantly inherited RP but who were characterised by a more generalised loss of rod function and early onset of night blindness (Ernst WJK, Lyness AL, personal communication). Erythrocyte osmotic fragility increases with age of the donor (3–5). We must therefore also consider the significantly lower mean age in males with the D-type lesion (Table 1). However, an approximate correction, based on the rate of increase in X-50 in normal males over the age range 26 to 40 years,[5] predicted a mean X-50 for D types of only 72±2 at 40 years of age.

Increased fragility was also evident in erythrocytes from females with multiplex RP and from carriers of the X-linked form of the disease. Although the latter do express a milder form of RP,[10] it is not possible from current knowledge to explain why they and not the more affected males show a change in the erythrocyte response. β Values were normal for both 'multiplex' females (304±23, n=5) and X-linked 'heterozygotes' (324±35, n=13).

Diverse factors interact to determine the membrane composition of circulating erythrocytes. Systems of potential relevance to the onset or progression of RP are lipid status[1,2] and the levels of free radical potentiating and scavenging agents. As regards the latter, erythrocytes and photoreceptors subserve functions that may expose them to internally generated free radicals with the subsequent production of activated oxygen. In erythrocytes this may arise from breakdown products of haemoglobin[13] and in photoreceptors from byproducts of the absorption of light by visual pigments or their photoproducts.[1,14,15] Vitamin E is the principal free radical scavenger and protectant for both systems,[13,16] and lack of the vitamin will lead to photoreceptor degeneration[17] and an increase in erythrocyte fragility.[18] However, other dysfunctions or deficiencies might have similar outcomes, and the actual cause(s) of the increased erythrocyte fragilities observed in RP patients in the present investigations must form the subject of subsequent research.

This study needed patients classified into RP subgroups, and for these we are indebted to our colleagues who passed on their unpublished results. We sincerely thank those who have volunteered or taken blood for us and, in particular, we are grateful for the encouragement and time given by Professor Geoffrey Arden, Professor Alan Bird, Dr Wojtek Ernst, and Miss A Lou Lyness.

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References

1 Fliesler SJ, Anderson RE. Chemistry and metabolism of lipids in the vertebrate retina. *Prog Lipid Res* 1983; **22:** 79–131.
2 Gottlieb MH. Rates of cholesterol exchange between human erythrocytes and plasma lipoproteins. *Biochim Biophys Acta* 1980; **600:** 530–41.
3 Detraglia M, Cook FB, Stasiw DM, Cerny LC. Erythrocyte fragility in aging. *Biochim Biophys Acta* 1974; **345:** 213–9.
4 Bowdler AJ, Dougherty RM, Bowdler NC. Age as a factor affecting erythrocyte osmotic fragility in males. *Gerontology* 1981; **27:** 224–31.
5 Hussain AA, Voaden MJ. Erythrocyte osmotic fragility in man: variation with age and sex. *Br J Haematol* 1984; **57:** 716–8.

6 Rifkind JM, Araki K, Hadley EC. The relationship between the osmotic fragility of human erythrocytes and cell age. *Arch Biochem Biophys* 1983; **222:** 582–9.

7 Jay M. On the heredity of retinitis pigmentosa. *Br J Ophthalmol* 1982; **66:** 405–16.

8 Voaden MJ, Hussain AA, Chan IPR. Studies on retinitis pigmentosa in man. I. Taurine and blood platelets. *Br J Ophthalmol* 1982; **66:** 771–5.

9 Ernst W, Faulkner DJ, Noble BA, Clover G. Psychophysical analysis of visual function in retinitis pigmentosa. *Dev Ophthalmol* 1981; **2:** 126–9.

10 Ernst W, Clover G, Faulkner DJ. X-Linked retinitis pigmentosa: reduced rod flicker sensitivity in heterozygous females. *Invest Ophthalmol Visual Sci* 1981; **20:** 812–6.

11 Arden GB, Carter RM, Hogg CR, *et al.* Rod and cone activity in patients with dominantly inherited retinitis pigmentosa; comparisons between psychophysical and electroretinographic measurements. *Br J Ophthalmol* 1983; **67:** 405–18.

12 Dacie JV, Lewis SM. *Practical haematology*. 5th ed. Edinburgh, London, New York: Churchill-Livingstone, 1975.

13 Paynter DI, Martin GB. Investigations of combined dietary deficiencies of copper, selenium and vitamin E in the rat. *Biol Trace Element Res* 1980; **2:** 175–91.

14 Kagan V, Shvedova A, Novikov K, Kozlov Y. Light induced free radical oxidation of membrane lipids in photoreceptors of frog retina *Biochim Biophys Acta* 1973; **300:** 76–9.

15 Wiegand RD, Giusto NM, Rapp LM, Anderson RE. Evidence for rod outer segment lipid peroxidation following constant illumination of the rat retina *Invest Ophthalmol Visual Sci* 1983; **24:** 1433–5.

16 Kagan VE, Lankin VZ, Shvedova AA, *et al.* Enzymic and non-enzymic systems protecting photoreceptor membranes against active forms of oxygen and lipid peroxides. *Bull Exp Biol Med* 1979; **88:** 856–8.

17 Robison WG Jr, Kuwabara T, Bieri JG. The roles of vitamin E and unsaturated fatty acids in the visual process. *Retina* 1982; **2:** 263–81.

18 Shapiro SS, Mott DJ. Alterations of enzymes in the red blood cell membrane in vitamin E deficiency. *Ann NY Acad Sci* 1982; **393:** 263–75.

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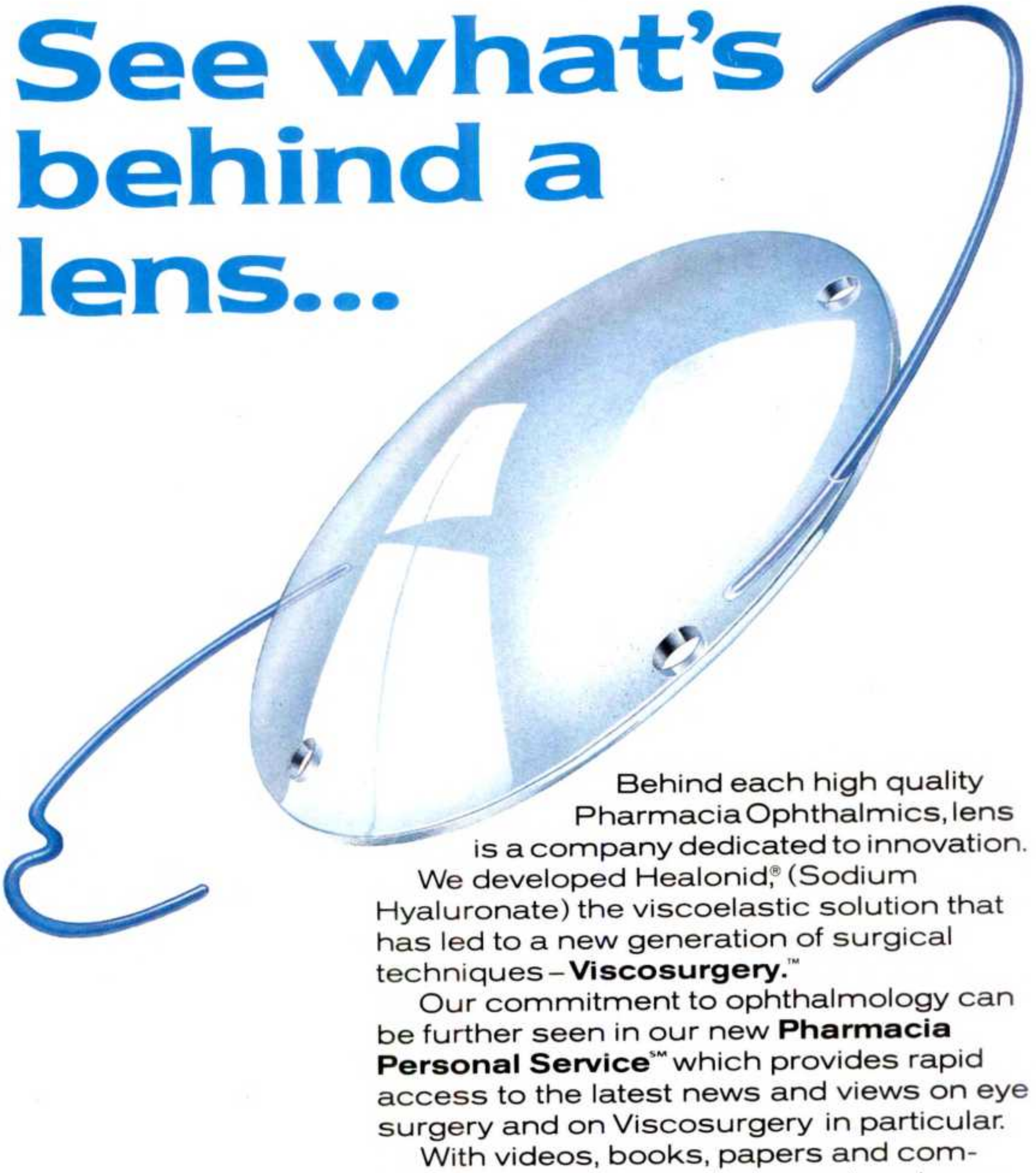

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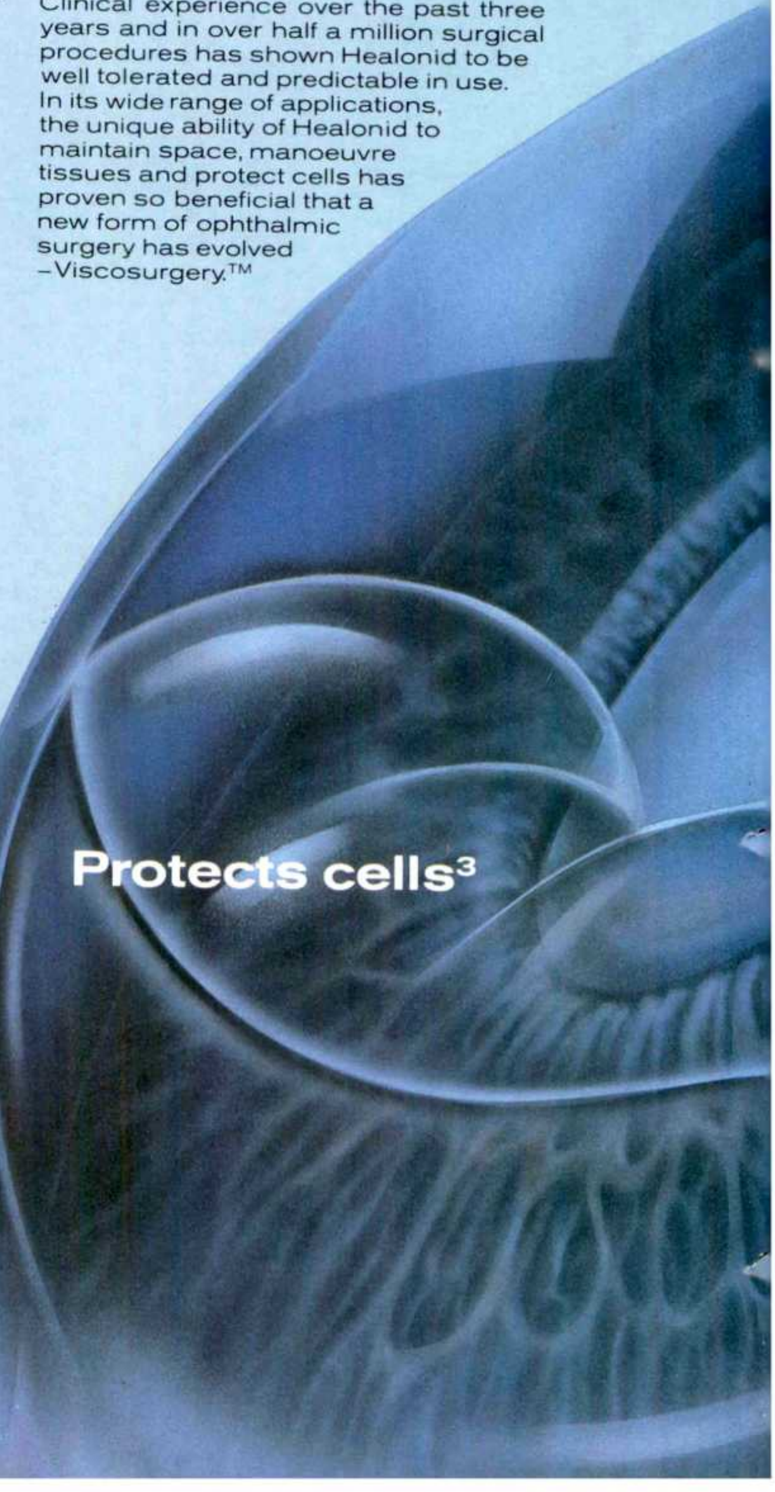

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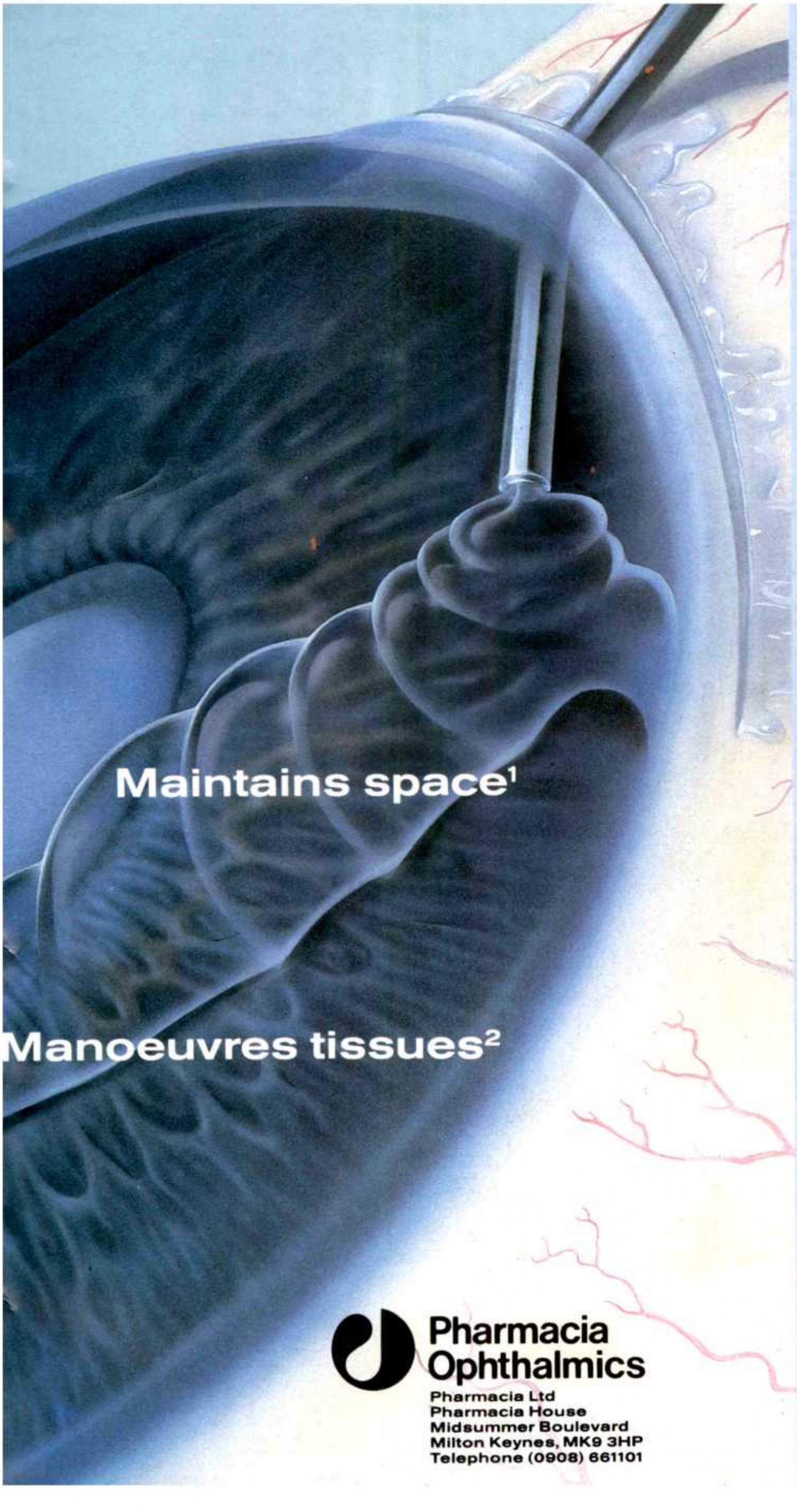

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PRESCRIBING TABLE

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INDICATIONS
Surgical procedures on the eye, including intraocular lens insertion, intra and extra capsular lens extraction, glaucoma surgery, corneal graft, surgery for accidental trauma, retinal detachment and vitreal replacement procedures.

DOSAGE AND ADMINISTRATION
The syringe is assembled and made ready for use according to the instruction sheet with each syringe. The indication for use will govern the timing and quantity of HEALONID used. See data sheet for Healonid Monograph.

PRECAUTIONS
The anterior chamber should not be overfilled with HEALONID, except in glaucoma surgery. At close of surgery some of the HEALONID should be removed by irrigation or aspiration. Intraocular pressure should be monitored during the post operative period and any excessive rises treated with appropriate therapy.

CONTRA-INDICATIONS, WARNINGS
There are no known contra-indications to HEALONID. Because the drug is extracted from avian tissues, despite rigorous purification procedures minute amounts of protein are present, and thus the remote possibility of idiosyncratic reactions remains.

ADVERSE REACTIONS
The drug is very well tolerated and the only untoward effect reported has been a transient rise in intraocular pressure in a few cases.

PHARMACEUTICAL PRECAUTIONS
Store at 2-8°C protected from light and freezing. Shelf life 3 years.

LEGAL CATEGORY POM.

PACKAGING QUANTITIES AND BASIC N.H.S. PRICE (6th April 1984) Disposable syringes containing 0.4ml £29.44 each.

FURTHER INFORMATION
HEALONID does not interfere with healing process. Its use may reduce incidence of synechiae and adhesions. Evidence from animal experiments indicates that HEALONID is no longer present in the anterior chamber six days after introduction.

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LACRI-LUBE *Presentation:* Sterile, bland, non-medicated ointment for topical administration to humans, containing white petrolatum mineral oil, non-ionic lanolin derivatives with chlorobutanol 0.5% as a preservative. *Uses:* Useful as adjunctive therapy to lubricate and protect the eye in conditions characterised by exposive keratitis, decreased corneal sensitivity, recurrent corneal erosions, and keratitis sicca. *Dosage and Administration:* For topical administration. Pull lower lid down to form pocket. Apply small amount as needed. *Contra-indications, etc:* No known contra-indications. *Pharmaceutical precautions:* Store away from heat. To avoid contamination during use, do not touch tip to any surface. *Legal Category:* P. *Package Quantities:* Available in 3.5g ophthalmic tubes. Basic NHS

British Journal of Ophthalmology, 1985, **69**, 129–135

Contrast attenuation characteristics of iris clipped intraocular lens implants in situ*

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SUMMARY In this study contrast thresholds were monitored over a wide range of spatial frequencies for patients with iris clipped implants or Fyodorov and Binkhorst types. These results were compared with those of an age matched normal group and attenuation characteristics derived for the implants and media environment alone. These results show that lenticular implants of this type can produce large reductions in contrast with a wide variety of transfer functions, for example, low pass, band reject, and band pass. These findings highlight the potential inadequacies of the assessment of the visual capabilities of these devices by acuity measures alone. We suggest that a more realistic and abbreviated approach should be based upon supplementing acuity assessment with monitoring of threshold sensitivity for a low, medium, and high spatial frequency sinewave grating.

Intraocular lens implants have been adopted as one of the treatments for aphakics since the technique was first employed by Ridley in 1949.[1] Binkhorst introduced his iris clipped lens in 1957.[2] Many modifications followed his design, which include the Fyodorov sputnik and Worst iris clipped lenses. The most prevalent intraocular lens (IOL) through the 1960s and up to 1978 was the iris clipped lens. At present iris clipped lenses are seldom used. The trend is towards using either anterior chamber or posterior chamber intraocular lenses. The United States Federal Drug Administration report[3] on IOLs showed that over one million of them have been implanted.

Kayes[4] reported that 85% of his first 100 consecutive medallion lens implants had visual acuities better than 6/12 five to seven years after surgery. Hurite and Lempert[5] stated that 93% of the 1442 cases of extracapsular cataract extraction with IOLs had 6/12 and better visual acuity. Statistics on visual acuities with IOLs presented by Stark matched those in the previous two studies.[3]

Reduced distance Snellen acuities through IOLs have been attributed to a variety of factors. They include: increasing patient age, surgical problems, postoperative complication, and adverse reactions.[3] Invariably vision has been assessed only with the use of conventional Snellen acuity charts. Contrast sensitivity measurement has been very successful in the evaluation of normal and abnormal visual function.[6-8] Its approach extends the present Snellen letter acuity assessment, which takes account only of high contrast acuity objects. The new approach to measurement of contrast sensitivity for object sizes within the resolution limit offers not only a more complete description of different types of visual loss but also a more sensitive one. It is hoped that these two factors will contribute to a method that correlates with perception. It is with this hope in mind that we have applied this approach to the assessment of the visual function of IOL implants. We find that some iris clipped IOL implants produce a wide variety of contrast attenuation that cannot be appreciated on the basis of acuity assessment alone.

Materials and methods

Vertical sinewave gratings of variable frequency and contrast were generated on the screen on an oscilloscope. The screen's mean luminance was set to 18 cd/m^2, and contrast was modulated about this luminance and adjusted by the patient with an 80 position switched logarithmic attenuator. Viewing distances varied from 570 cm for high spatial frequencies to 114 cm for low spatial frequencies. The method of adjustment was used to set thresholds. The patient's task was to respond when he first discerned non-uniformity of a field presented to him. Five thresholds were obtained for each of the predetermined grating frequencies. These patients were seen between three months and two years after surgery and refracted carefully for residual refractive errors. The IOL implants were inserted by one of us (P.D.W.) and were of either the Fyodorov or Binkhorst iris clipped type. Both Snellen acuities and contrast sensitivity functions were obtained for each subject (10 eyes). Visual acuities were determined with a log MAR chart[9] and converted into their Snellen equivalents (see Table 1).

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*Presented in part at the meeting of the Association of Research in Vision and Ophthalmology in Sarasota, Florida, in May 1981.

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Results

The contrast sensitivity assessment of 10 normal eyes is displayed in Fig. 1. The 95% confidence limit for normal vision extends to cover approximately a factor of two in contrast sensitivity at each spatial frequency. These subjects were age matched to our patient sample and were also similarly inexperienced in psychophysical tests. These results showed that, even though any one subject's result could be repeated to an accuracy of ±2 dB of contrast sensitivity (±25%), there was a genuine range of absolute variability between eyes.

Since two of our patients were uniocularly pseudophakic with a normal fellow eye, we had the opportunity to compare their normal eye's response with that of our normal, matched control group. In Fig. 2 the 95% confidence limits of our normal population, shown as a shaded area, is compared with the results for normal eyes (unfilled symbols) and eyes with intraocular implants. The results for the two normal eyes of our patient group compared well with the mean of our normal population.

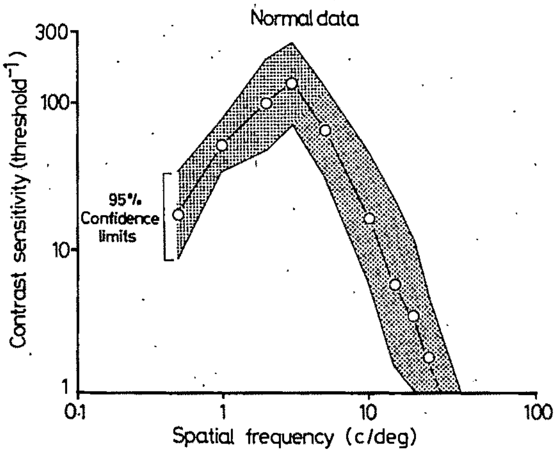

Fig. 1 *The relationship between contrast sensitivity (threshold^{-1}) is plotted against spatial frequency (cycles of the grating per visual degree) for grating stimuli with a sinusoidal luminance profile. The data for 10 normal subjects, whose ages are matched to our patient population, are shown. Open symbols show the mean results. The stippled area represents ±95% confidence limits (±2 SD).*

The contrast sensitivity results through IOL lenses were made between three months and two years after implantation to minimise the effects of postsurgical trauma or cystoid macular oedema known to occur sometimes after surgery. An ophthalmological assessment of each patient made by one of us (P.D.W.) at the time of testing indicated no obvious corneal oedema or cystoid macular oedema except in patient six, who showed postsurgical cystoid macular oedema.

Seven of our patients showed large and highly significant losses of contrast sensitivity. Unexpectedly the form of the loss in sensitivity was not of a unitary type. In patients 2 and 5 the contrast sensitivity loss was minimal at low spatial frequencies and increased with increasing spatial frequency. In patients 3, 4, and 8 the contrast sensitivity loss was restricted mainly to mid spatial frequencies. Sensitivity was close to normal for very high (40 c/deg) and very low (0·5 c/deg) spatial frequencies. In the case of patient 6, who suffered postsurgical complications, contrast sensitivity losses were seen for all spatial frequencies, but intermediate spatial frequencies were relatively less affected.

The selective loss of contrast sensitivity for intermediate spatial frequencies, which represented the largest response category, could not be detected by the measurement of grating acuity alone. In Fig. 3 the loss of contrast sensitivity at 3 c/deg is compared with loss of grating acuity. It is obvious (as it is from the results in Fig. 2) that, although there is good correlation between these two measures, there is a significant non-zero y intercept. This means that grating acuity began to change only after thresholds for mid spatial frequencies were raised by a factor of approximately three. For contrast losses of less than a factor of three grating acuity was a poor predictor of contrast transmission at intermediate spatial frequencies. Although only two Binkhorst implants were tested, there seemed to be no obvious difference between the Fyodorov and Binkhorst types compared with the great variety of responses with any one implant type. Table 1 gives the Snellen acuity of all patients. It is clear from a comparison of these acuities with the contrast loss in Fig. 2 that Snellen acuity, like grating acuity, was also a poor predictor of the overall visual quality of the implant.

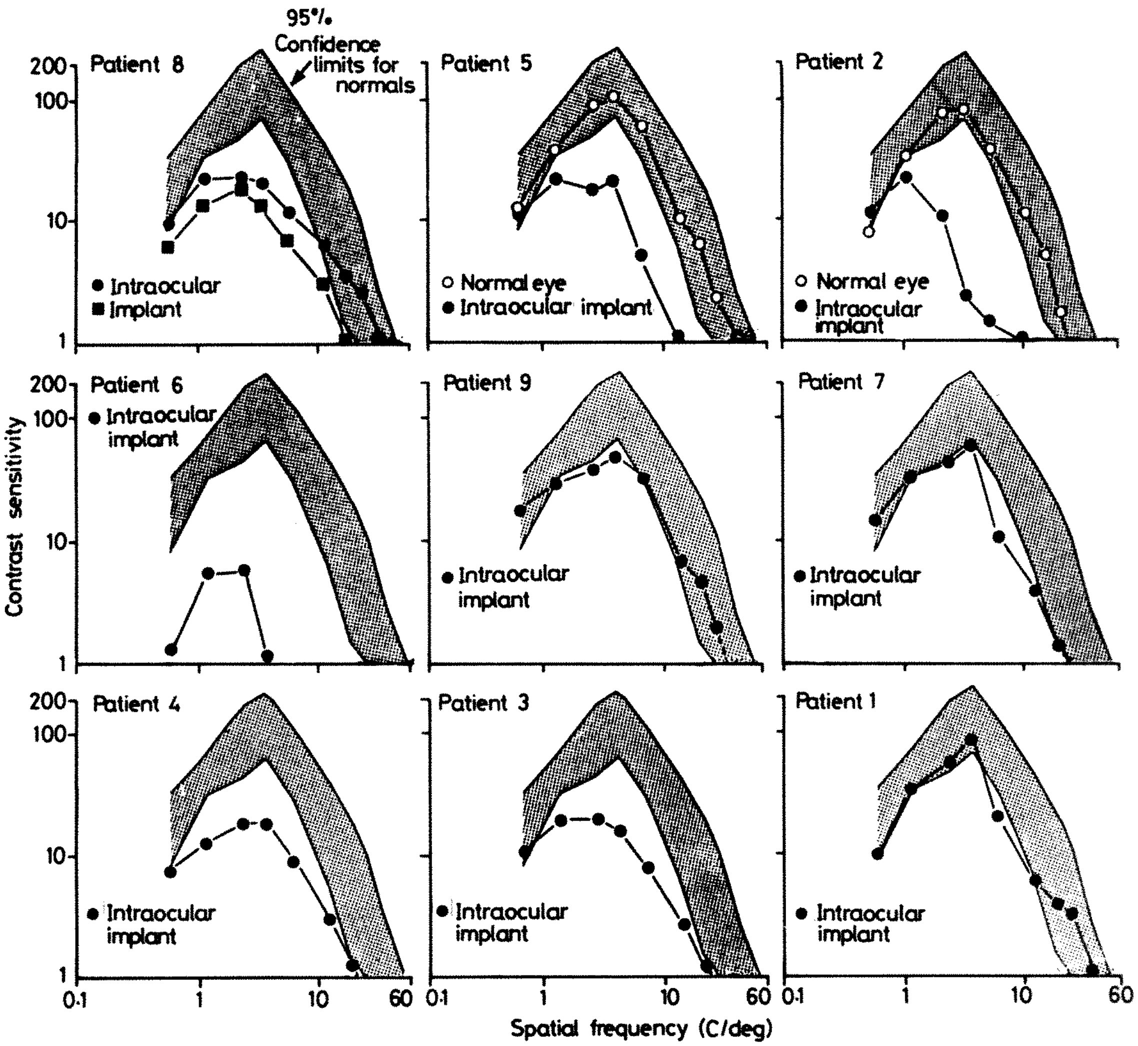

Fig. 2 *Contrast sensitivity functions are shown for the normal (○) eyes and eyes with intraocular implants (●). These are compared with the 95% confidence limits for age matched normals. The losses in contrast sensitivity for the intraocular implant are large and vary considerably from patient to patient.*

The contrast filtering properties of the iris clipped IOL implant and media environment could be approximately calculated from the present results by taking the ratio of sensitivity for the normal intact eye and the lens implant eye at different spatial frequencies. The wide variety of contrast filtering is seen in these results (Fig. 4). To obtain these results we used the means of the results of the normal eyes. Since there is a range of sensitivity for normal eyes, the lower limit of the 95% confidence limit of normal sensitivity is seen in Fig. 4 as a horizontal dashed line. Results falling above this line (e.g., patient 1), while being below the normal mean, are not outside the 95% confidence limits of normal vision and so should be viewed as suspicious rather than definitely abnormal.

The filtering properties of these two IOL types in situ fell into three categories: low pass, band reject, and band pass. In the low pass cases contrast was attenuated more at higher spatial frequencies. This is similar to optical blur. In the band reject cases contrast was selectively lost for only intermediate spatial frequencies. In the band pass case contrast was lost at low and high spatial frequencies but was relatively spared for intermediate spatial frequencies.

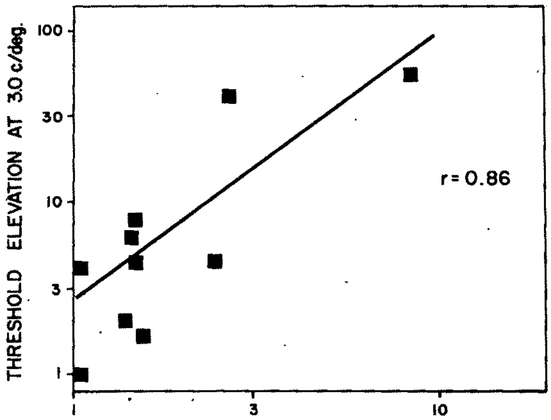

Fig. 3 *Correlation between the contrast threshold loss at 3c/deg and the grating acuity is plotted for the 10 eyes with intraocular implants. The non-zero y intercept indicates that grating acuity is not a very good predictor of contrast loss at intermediate spatial frequencies in some cases.*

Discussion

The present clinical assessment of the optical performance of IOL implants in situ is accomplished by the measurement of visual acuity and reports by the patient. This is a very rudimentary assessment when one considers the accuracy with which the optical quality of isolated lenses can be specified with modulation transfer function (MTF) procedures. In this latter procedure contrast transmission can be accurately assessed for sine wave gratings of a wide range of spatial frequencies, and the exact form of the contrast loss (that is, its filtering characteristics) can be obtained. Since the final court of appeal for IOLs is their optical performance in situ, we have adopted a psychophysical procedure analogous to the now well established MTF optical assessment procedure.

Table 1 *Visual acuities of 9 patients with IOLs*

Patient	*Visual acuities*		*Type of IOL*
	OD	*OS*	
1	6/9	6/7·5	OD Fyodorov
2	6/9	6/30	OS Fyodorov
3	6/7·5	6/6	OD Fyodorov
4	6/18	6/18	OS Fyodorov
5	6/18	6/18	OS Fyodorov
6	6/96	6/15	OD Binkhorst
7	6/38	6/7·5	OD Binkhorst
8	6/9	6/38	OU Fyodorov
9	6/6	6/6	OS Fyodorov

Snellen visual acuities are listed for 10 patients with IOLs. The acuity chart was calibrated in log MAR (logarithmic minimum angular resolution) units of 0·1 log intervals. According to this new and useful scheme the acuity of each line on the chart changes by a constant factor (for example, 1·26). We used this chart because of its greater accuracy, but we have converted these to Snellen notation for ease of comparison. Since the acuity step is finer than the usual clinical chart, our converted acuities result in some unfamiliar Snellen fractions.

Our psychophysical procedure involves a comparison between the measurement of contrast thresholds for various spatial frequency sinewave gratings for normal eyes and those with implanted lenses. The ratio of these sensitivities across spatial frequency gives a psychophysical estimate of the modulation transfer properties of the implants and media environment itself. This procedure relies upon the assumption that any differences between normal eyes and eyes with lens implants are due to the implants and media environment. Aside from patient 6, none of the patients showed any ophthalmologically detectable postsurgical complications.

Interestingly we found that the contrast loss produced by these two examples of iris clipped lenses was considerable and variable in form. In most cases the conventional acuity test would not have detected this (see Table 1), and unless the patient had one normal eye with which to compare it might not have been easily identified by the patient. For some patients contrast was lost only at high spatial frequencies (low pass). This is similar to blur and thus likely to be the only type of transmission loss detected and adequately assessed by acuity tests. For another group of patients contrast was lost selectively at mid spatial frequencies. This would not be detected at all by standard acuity tests. In the one case in which there were postsurgical complications (patient 6) contrast was lost at low and high spatial frequencies but relatively spared for intermediate spatial frequencies. The extent of the visual loss in this case would also have been grossly underestimated by acuity tests. The variety and extent of the contrast loss due to these intraocular implants (some loss is hidden and restricted to only mid spatial frequencies) argues strongly for assessment of visual performance of these patients to include more than just the limit of resolution (acuity tests).

As is the case in all visual loss due to optical anomalies, any threshold loss has similar consequences for suprathreshold contrast targets. For example, if the contrast threshold is raised by a factor of 10 due to optical degradation of an intraocular implant, then it is also true that any suprathreshold contrast will be similarly reduced. Thus a 100% contrast target will be reduced to 10%. This means that the contrast loss at threshold reported here will have important consequences for visual performance at all, (including high) contrast levels. In order to estimate the possible perceptual consequences of the contrast losses observed with these implants a photo-

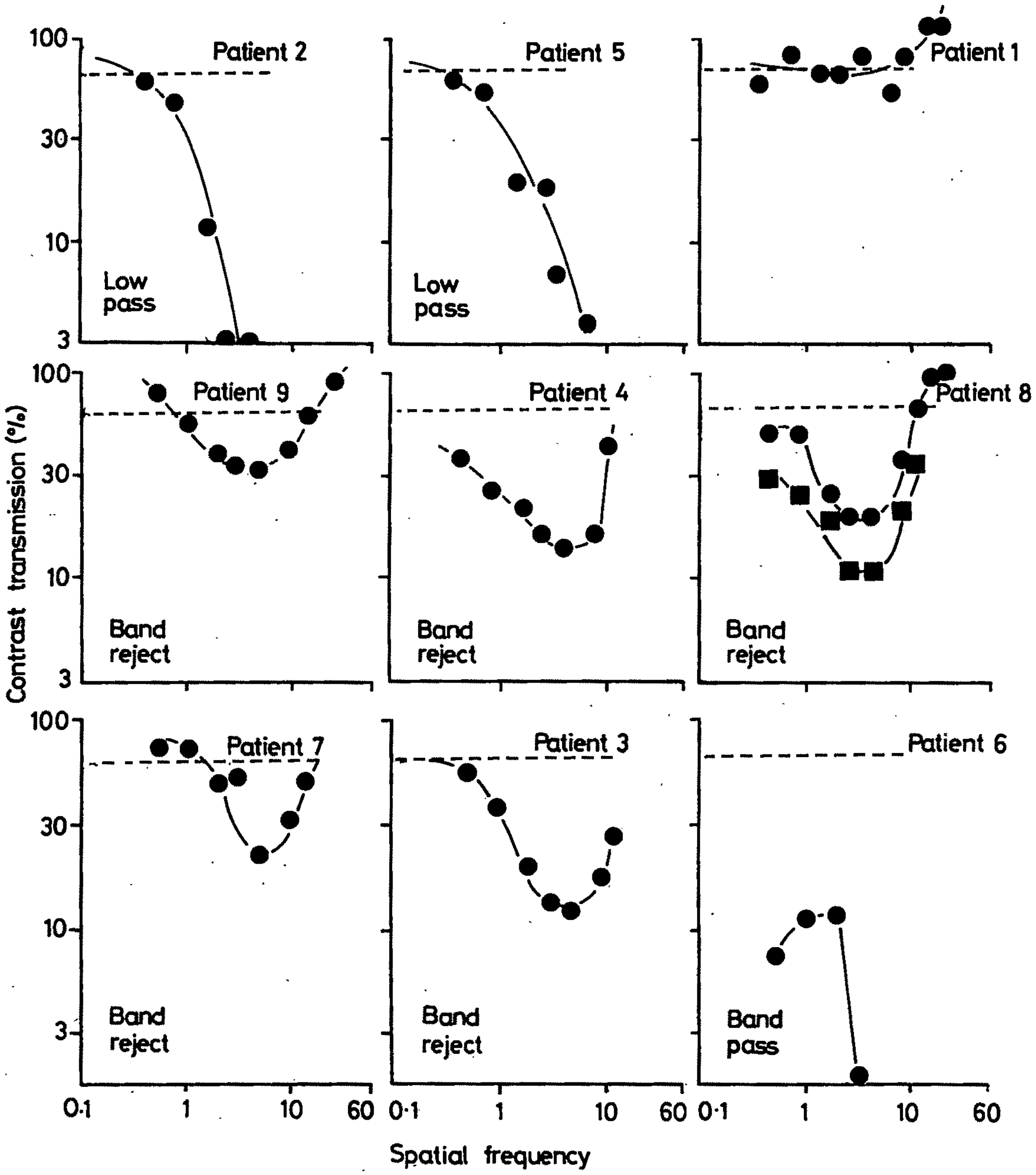

Fig. 4 *The average contrast sensitivity results shown in Fig. 2 for the 10 normal eyes have been divided by the contrast sensitivity of the implant eye at each spatial frequency to obtain the contrast transmission characteristics (% transmission) of the intraocular implant. The dash line indicates the lower boundary of the 95% confidence limit of the normal population. Results above the dash line are not significantly different (patient 1) from the normal population. The contrast transmission properties fall into three categories: low pass, band reject, and band pass (see text).*

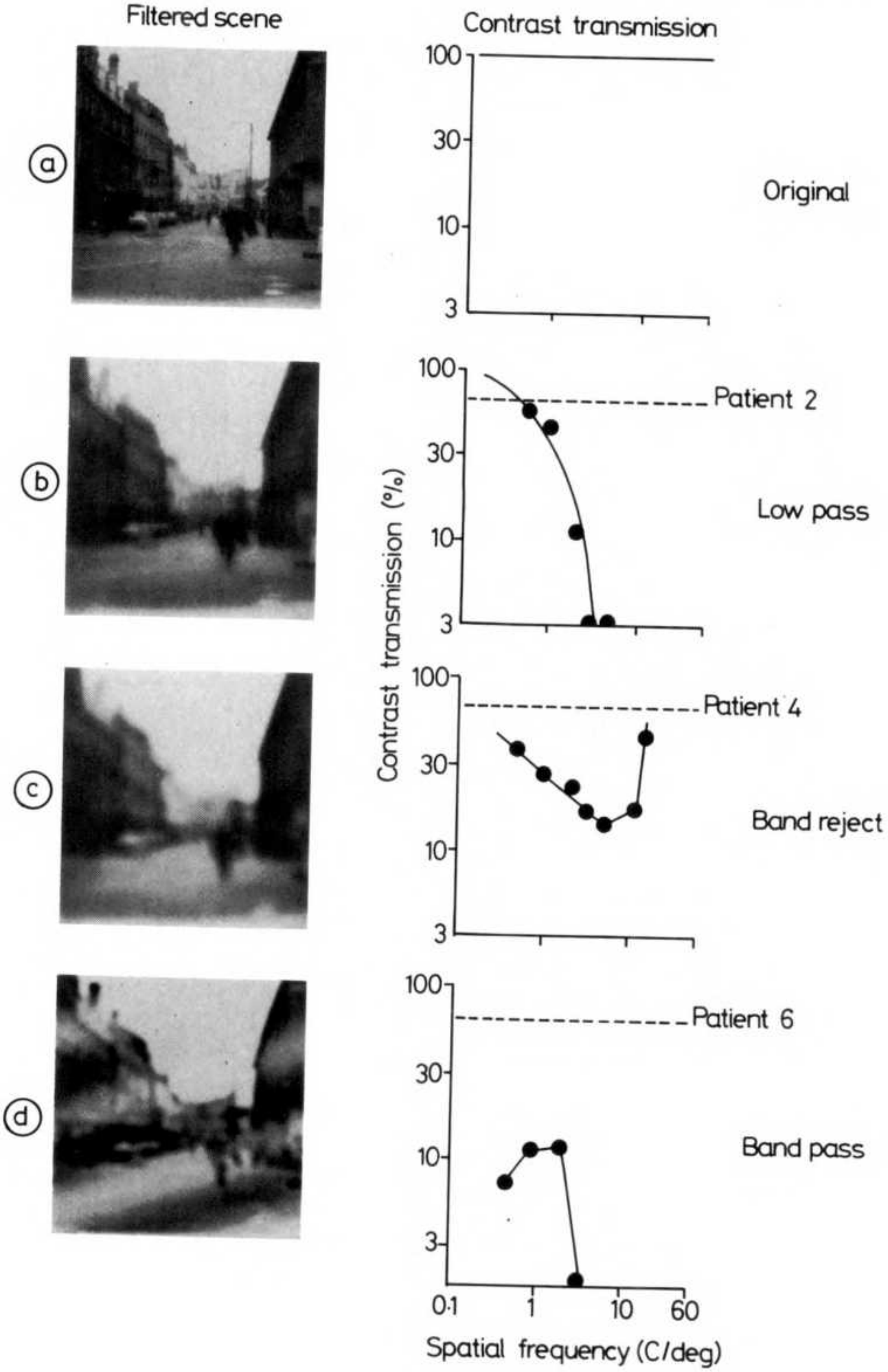
Filtered scene
Contrast transmission
a
Original
b
Low pass
Patient 2
c
Band reject
Patient 4
d
Band pass
Patient 6
100
30
10
3
Contrast transmission (%)
0·1
1
10
60
Spatial frequency (C/deg)

Fig. 5 *An outdoor scene* (A) *is digitally filtered in accordance with the three types of contrast loss shown to occur as a result of IOL implant. Whereas the low pass* (B) *and band reject* (C) *properties result from the IOL and media environment, the band pass properties* (D) *were contaminated with post-surgical macular oedema. These pictures give only a crude indication of the perceptual consequences of measured losses in contrast.*

graph of a visual scene was spatially filtered in accordance with the three different types of contrast loss reported here (Fig. 5). Fig. 5A was digitally sampled and reconstructed without any modification to show the quality of the filtering process itself. Fig. 5B, 5C, 5D represent contrast losses of spatial frequencies in accordance with the three types (low pass, band reject, and band pass) of transmission loss found in the present study.

Note that in all three cases there is a significant loss in optical quality. Patient 4, whose transplant displayed band reject transmission properties, has the least severely affected acuity (Snellen 6/18; grating acuity 20 c/deg). Since contrast is only lost for intermediate spatial frequencies much of the high frequency or fine detail is present in the filtered image, but it is difficult to discern objects of intermediate size. Patients 2 and 6 show very different transmission properties, but their grating acuities are identical (3 c/deg). Their filtered images are noticeably different as are their Snellen acuities (patient 2, 6/30; patient 6, 6/96). The patchy nature of patient 6's filtered image is because of an added loss of contrast at low spatial frequencies. These pictures demonstrate the diversity of perceptual effects from the different filtering properties of these lenses.

CONCLUSION

In conclusion our results show that contrast loss can be severe, particularly when there are surgical complications. There can be many different types of contrast loss with IOLs, and these can be adequately assessed by our measuring thresholds at high, low, or intermediate spatial frequencies. Snellen acuity measurements are not adequate to detect these losses or to appreciate their perceptual consequences. We advise that contrast threshold measurements should be used to assess the effectiveness of these devices for low, medium, and high spatial frequencies.

This study is supported in part by the Natural Sciences and Engineering Research Council of Canada (Grant No A3449), the Medical Research Council of Great Britain, and the Wellcome Trust. We thank Mr I Piotrowski for producing the photographic plates. RFH is a Wellcome senior lecturer.

References

1 Ridley H. Intraocular acrylic lenses. *Trans Ophthalmol Soc UK* 1951; **71:** 617–21.
2 Nordlohne ME. *The intraocular implant lens: development and results with special reference to the Binkhorst lens.* 2nd ed. Baltimore: Williams and Wilkins, 1975.
3 Stark W. The FDA report on intraocular lenses. *Ophthalmology* 1983; **90:** 311–7.
4 Kayes J. Recent experience in lens implantation. Presented at the Washington University Eye Alumni Meeting, St Louis, April 1981. Cited by Bobrow JG, Drews RC, in 'Iris clip lens implantation.' In: Langton RHS, ed. *Intraocular lens implantation.* International Ophthalmology Clinics. Boston: Little, Brown, 1981.
5 Hurite FG, Lempert SL. Iridocapsular intraocular lens and extracapsular cataract surgery. In Langton RHS, ed. *Intraocular lens implantation.* International Ophthalmology Clinics. Boston: Little, Brown, 1981.
6 Campbell FW, Green DG. Optical and retinal factors effecting visual resolution. *J Physiol (Lond)* 1965; **181:** 576–93.
7 Hess R, Woo G. Vision through cataracts. *Invest Ophthalmol Visual Sci* 1978; **17:** 428–35.
8 Woo G, Dalizel C. A pilot study of contrast sensitivity assessment of CAM treatment of amblyopia. *Acta Ophthalmol (Kbh)* 1981; **59:** 35–7.

British Journal of Ophthalmology, 1985, **69**, 136–142

Impaired contrast sensitivity in diabetic patients with and without retinopathy: a new technique for rapid assessment

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SUMMARY A simple technique is described for assessing the sensitivity of the human visual system to gratings at threshold contrast. The technique has advantages for clinical use in that it is (1) inexpensive, (2) quick to administer, (3) portable, and (4) relatively free from bias. Forty-two diabetic patients and 84 normal controls have been tested. Fifteen diabetic patients (6/20 with retinopathy and 9/22 without) had test scores more than two standard deviations below the norm for age-matched controls.

The threshold contrast at which a pattern of stripes is just visible is a measure of visual function that has recently received great attention. It differs from conventional acuity in several respects[1-3] and can pick up deficits not detected by more conventional measures in lens[4-5] and retinal[6-10] pathology, glaucoma,[11-15] retrobulbar neuritis,[16-18] and other disorders.[3 19-21] The contrast threshold is best measured by electronically varying the contrast of a pattern on the surface of a cathode ray tube,[22-24] but such a system is not convenient for widespread clinical use. Arden[25] has therefore devised a test consisting of gratings printed on cards. The contrast of the gratings decreases along the length of the stripes. The subject covers the grating with a card, exposing the lowest contrast first, until he reports that he can see the stripes. The test has its clinical utility[11 15 25] but is expensive to produce, costing about $200 (£135) to purchase. This method of measuring contrast is open to the objection that strategic differences in criterion may have a considerable and indeterminate influence. By cutting the Arden plates into discs Vaegan and Halliday[26] devised a printed contrast sensitivity test with four-alternative forced choice format, in which subjects were required to report the orientation of the stripes.

The aim of this article is to describe a simple two-alternative forced choice test which is both quick to administer and cheap to reproduce. It differs from the other tests in seeking to obtain a rapid but reliable estimate of the detectability of gratings with just one spatial frequency, namely 4 cycles/degree, the frequency at which the sensitivity of the visual system is near its maximum.[23] The orientation of the gratings is usually horizontal but can be varied if required.

Arden,[27] Ghafour *et al.*,[6] Hirsch and Puklin,[28] and Hyvärinen *et al.*[7] have reported that contrast sensitivity is reduced in diabetic patients. Our test was developed to investigate diabetic patients with normal Snellen acuity. All the patients received a complete ophthalmological examination on the basis of which they were divided into two groups: those with and those without retinopathy.

Details of the test

The test comprises a series of 10 pairs of square plates. The pairs are presented with one plate above the other, the grating in the top or the bottom plate at random. The observer is forced to choose whether the top or the bottom plate contains the grating, guessing if necessary. The first pair of the series has a grating with high contrast which serves as an example, and the gratings in subsequent plates

Correspondence to Dr A J Wilkins.

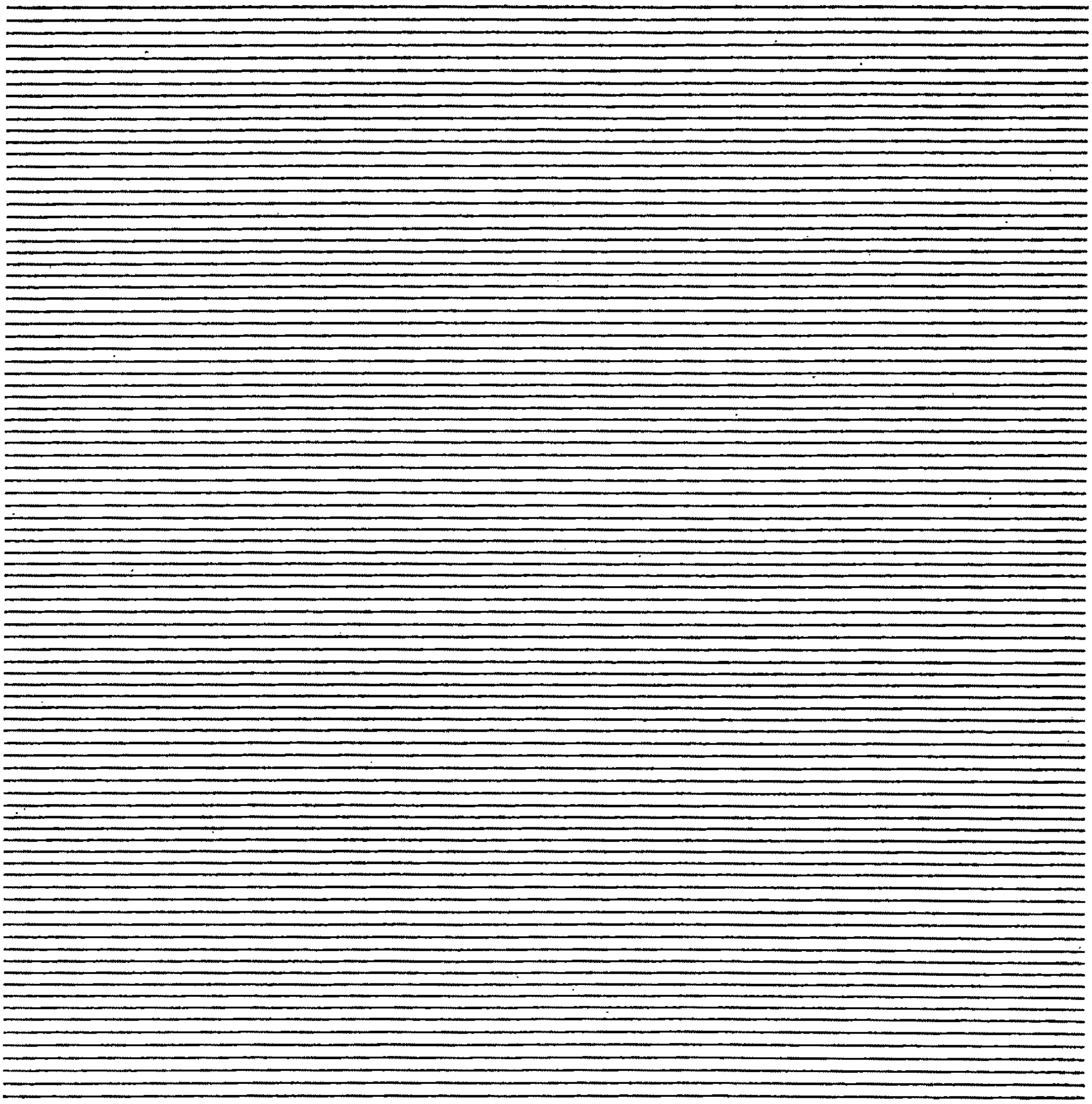

Fig. 1 *An apparent grating with square-wave luminance profile resulting from variations in the spacing of the lines, suitable for viewing at 6 m.*

decrease in contrast. The plates are designed to be viewed at 6 m, at which distance they subtend 2° by 2° and have a spatial frequency of 4 cycles/degree. (In the present study the plates were reduced in size by 33% by means of electrostatic photo-reduction so that they could be viewed at 5 m, the distance at which visual acuity is usually measured in Italy. They subtended 1·5°×1·5°.)

The test plates are printed from computer-generated plots of parallel lines that vary in their separation and thus their density, as shown in Fig. 1. They have a luminance profile that has been represented schematically in Fig. 2.

At the distance from which the plates are viewed the individual lines can no longer be seen. The variations in line density are, however, visible. These variations in density themselves comprise stripes (apparent gratings with a square-wave luminance

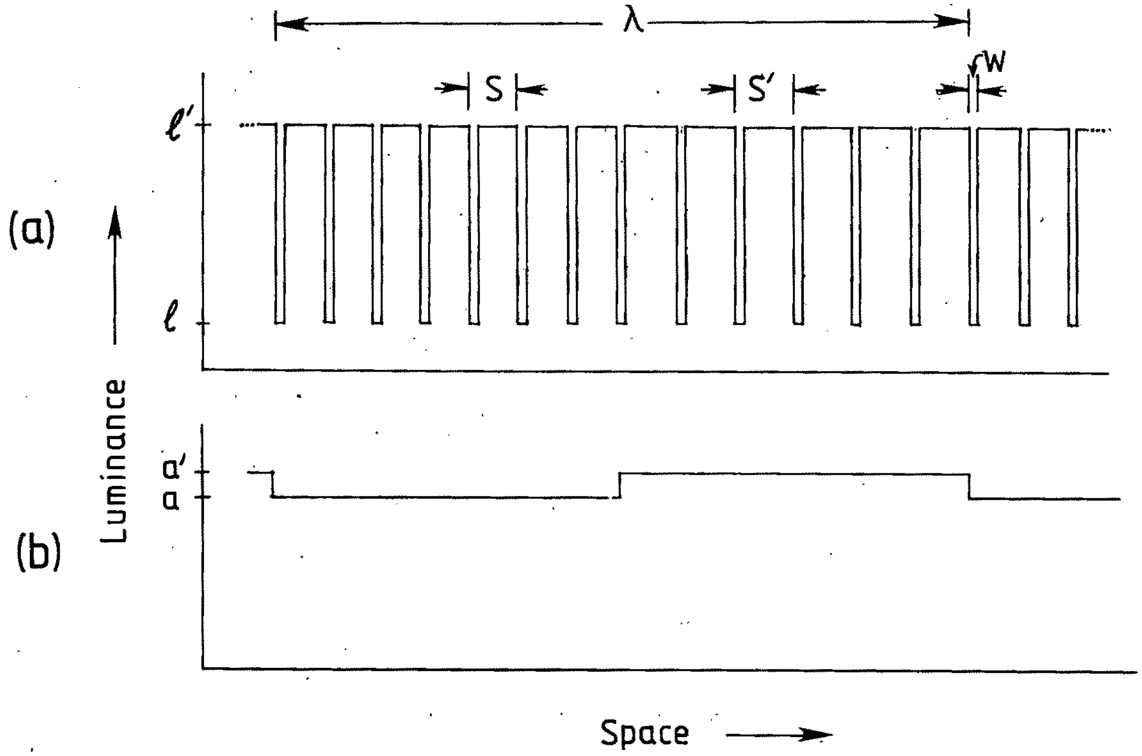

Fig. 2a *Luminance profile of the grating shown in Fig. 1. The ink in which it is printed has a luminace of l, and the paper a luminance of l'. The spacing of the lines (width w) alternates between s and s' every λ units of length so as to change the line density with a square-wave luminance profile shown in Fig. 2b. When viewed from a distance at which the component lines cannot be resolved, the grating has an apparent contrast of (a' − a)/(a' + a) and a spatial frequency of l/λ.*

profile and a period of 36 mm—i.e., a spatial frequency of 28 cycles/m. The Michelson contrast of the apparent grating is given by the expression

$$(a'-a)/(a'+a)$$

where a and a' are the mean reflectances of the closely spaced and widely spaced lines respectively. The mean reflectance is determined by the reflectance of the paper, the reflectance of the ink, and the width and spacing of the lines. It can be shown that the above expression reduces to

$$\frac{cw\,(s'-s)}{(1+c)\,ss'-cw\,(s+s')}$$

where c is the contrast of the ink on the paper, w is the width of the lines, and s' and s are the maximum and minimum separation of the lines respectively (see Fig. 2). From the above expression it can be shown that the contrast of the apparent grating will change little with changes in the contrast of the ink on the page or the width of the individual lines, factors that might be expected to vary with printing impression. For values of the parameters within the range used, changes of 10% in the width of the lines or the contrast of the ink on the page change the contrast of the apparent grating by a similar amount. Contrast sensitivity in normal persons may vary by a factor of 2 or more, for example, between 0·5% and 1%. If an apparent grating is made with a contrast of 0·5%, and the line width or contrast of the ink alters by, say, 20% (which is more than would occur in practice), then the contrast of the apparent grating would be expected to vary between 0·4% and 0·6%, depending on the direction of variation in these parameters and the extent to which they covaried. The changes in apparent contrast from one printing impression to another are therefore likely to have little effect on the percentile scores obtained by the test and thus on its ability to discriminate normal from abnormal vision. The contrast of the apparent grating is critically determined by the separation of successive lines, and this should vary little with printing impression.

As mentioned above, the test plates were reduced for use at 5 m. The line separations are shown after

Table 1 *Reduced version of low contrast plates for use at 5 m*

Plate pair	*Separation (mm)**		*Nominal contrast (%)*
	Maximum	*Minimum*	
1	1·57	1·33	2·07
2	1·51	1·33	1·62
3	1·45	1·33	1·13
4	1·43	1·33	0·96
5	1·40	1·33	0·69
6	1·39	1·33	0·59
7	1·37	1·33	0·40
8	1·36	1·33	0·30
9	1·35	1·33	0·20
Blank	1·33	1·33	0·00

*Values calculated on the basis of the photoreduction.

Table 2 *Revised version of low contrast plates for use at 6 m*

Plate pair	*Separation (mm)*		*Nominal contrast (%)*
	Maximum	*Minimum*	
1	2·22	1·38	4·76
2	2·06	1·54	2·82
3	1·96	1·64	1·71
4	1·90	1·70	1·06
5	1·86	1·74	0·64
6	1·84	1·76	0·42
7	1·82	1·78	0·21
Blank	1·80	1·80	0·00

reduction in Table 1, together with a nominal value for the contrast of the apparent grating based on a value of 0·7 for the contrast of the ink on the paper and a value of 0·35 mm for the width of the lines. The separation of lines was chosen so that the apparent contrast of successive gratings decreased with intervals on a logarithmic scale that were as evenly spaced as the technical constraints would allow. (In the light of experience with the test a revised version has now been produced for use at 6 m, and the details of this test are shown in Table 2.)

The contrast of the apparent grating was measured for the photocopies of the first two test plates by means of a bifurcated optic fibre to project light to, and collect light from, a rectangular portion of the plate measuring 10×70 mm, orientated with the long axis parallel to the lines. The contrasts of the first two plates were within 0·2 of the values tabulated. The nominal values of contrast may therefore be taken to be reasonable estimates of the actual values.

Subjects and methods

Forty-two diabetic patients, 22 male and 20 female, aged 12–75 and 84 normal volunteers, 52 male and 32 female, aged 14–68 took part in the study. All subjects (patients and volunteers) were selected as having a Snellen acuity of 1·0 or more (5/5 as it is usually measured in Italy), after correction where necessary (no subject was amblyopic). The diabetic patients were chosen from those patients who regularly attended the eye clinic at L Sacco Hospital, University of Milan. Hospital staff, medical students, and patients' relatives volunteered to act as unpaid (age matched) control subjects.

All subjects underwent a full ophthalmological investigation which included Snellen acuity, slit-lamp examination, tonometry, and direct and indirect ophthalmoscopy. The patients were also examined by Goldmann lens biomicroscopy and fluorescein angiography. In none of the subjects who were admitted to the study could we detect any ocular alteration such as glaucoma, cataract, or minimal opacities, although 34 normals and 24 patients needed optical correction.

Twenty-two patients (11 male and 11 female aged 17–72, mean 46) had no detectable retinopathy. Fluorescein angiography showed no evidence of microaneurysms, haemorrhages, soft or hard exudates, areas of capillary non-perfusion, or leakage of vessels at the posterior pole or in the periphery of either eye. The length of the patients' illness ranged from 1 to 22 years (mean 7 years). Eight were affected by type I diabetes mellitus and 14 by type II.[29]

Twenty patients (11 male and 9 female, aged 16–75, mean 42) had retinopathy. Nineteen had a background retinopathy (microaneurysms, scattered haemorrhages, and a few hard exudates at the posterior pole) and one, a male aged 48, had proliferative retinopathy with an initial peripheral neovascularisation. In all but one, a 17-year-old female, the retinopathy was bilateral. In three there was an initial macular oedema with retention of good visual acuity. Two other patients presented areas of capillary non-perfusion at the periphery of the fundus. The contrast test was administered prior to argon laser photocoagulation when this was required. The length of the patients' illness ranged from 3 to 31 years (mean 15 years). Twelve patients were affected by type I and eight by type II diabetes.

The test plates were mounted on the pages of a spiral bound book. The book was fixed on a wooden stand at a viewing distance of 5 m and illuminated by a filament lamp (60 watts at a distance of 1·5 m) so that the mean luminance was about 50 cd/m^2. Care was taken to ensure that the position of the lamp, plates, and eye of the observer did not vary from one test to the next. The series of plates was presented three times. Eyes were tested in random order.

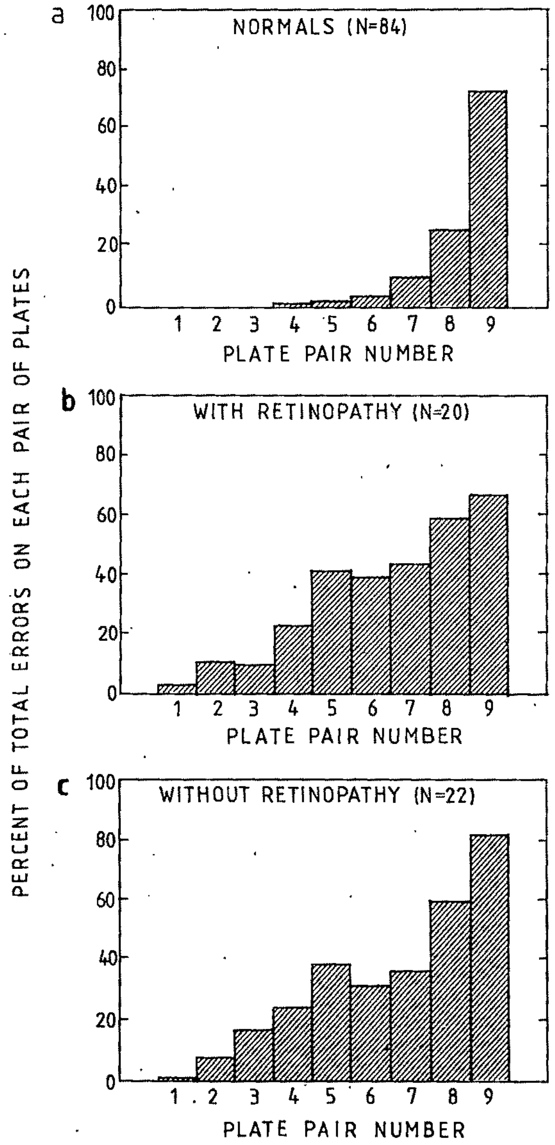

Fig. 3 *Histogram of the number of errors made on stimulus pairs 1–9, for* (a) *normal control subjects,* (b) *diabetic patients with and* (c) *without retinopathy.*

The data for control subjects and patients were collected over the same period of time (about one year), and so any degradation of the plates that may have occurred could not have accounted for the differences between groups.

Results

In Fig. 3 the errors made by each group of subjects are shown separately for the nine pairs of test plates. From these histograms it is evident that on the pair of plates with the lowest contrast stimulus (pair number 9), subjects were not responding to the grating but to some aspect of the blank stimulus that resembled a grating (see Details of test). Were subjects responding at random, that is, appropriately for a grating they could not see; an error rate of about 50% would have been expected. Both normal subjects and patient groups responded with an overall error rate of about 75%, a rate significantly above chance. The responses to this pair of stimuli have been included in the analyses that follow because when they were removed the findings were not appreciably changed.

An initial set of analyses was performed on the total number of errors made by the two eyes on the three presentations of the test. Preliminary analyses of the data for normal subjects failed to reveal any sex differences but indicated an increase in errors with age, maximal over the age of 50. On the basis of these analyses the normal subjects were divided into three groups: 40 young (14–29, mean 22): 30 middle-aged (31–48, mean 40); 14 older (50–68, mean 59). The total error scores for both eyes averaged: 5·2 (SD 2·5), 7·3 (SD 5·2), and 11·0 (SD 7·6) for the three age groups respectively. On the basis that the percentage correct responses to plates 7 and 8 were respectively slightly more and slightly less than 75%, the mean contrast sensitivity (reciprocal of contrast threshold) for the group was between 250 and 330. For the patients the total error scores were converted to z scores by comparison with the appropriate age matched control group. Six of the 20 patients with retinopathy and nine of the 22 without had total error scores more than 2 standard deviations above the mean for the normals (see Table 3). There were no differences between the error scores for patients with type I and type II diabetes or those with and without retinopathy. The lower proportion of older patients with poor z scores is presumably because of the

Table 3 *Number of patients in each age group (size n) with and without retinopathy, whose error scores were more than 2 standard deviations above the mean for age matched controls. The scores were calculated on the basis of the total errors for both eyes on all trials, total errors for the worst eye on all trials, and errors for both eyes on the first trial only*

Age range	*With retinopathy*			*n*	*Without retinopathy*			*n*
	Total	*Worst*	*First*		*Total*	*Worst*	*First*	
10–29	1	1	1	2	5	5	5	7
30–49	4	4	4	6	3	4	2	5
50+	1	1	2	12	1	1	1	10
Total	6	6	7	20	9	10	8	22

greater variability between normal individuals in the older age group.

Similar analyses were also performed using the scores for the eye with the highest error score, and these produced closely comparable results (see Table 3).

In both of these analyses the correlation between the number of errors and the length of the disease was positive (Spearman rank correlation between 0·2 and 0·3) but did not approach significance, regardless of the presence or absence of retinopathy.

When the error scores for the two eyes on the first presentation of the test were considered separately, they were highly correlated with the total errors on all presentations (normals: $r_s0{\cdot}85$; patients: $r_s0{\cdot}93$). As can be seen from a comparison of the data in Table 3, a single presentation of the test to each eye (taking about one minute per eye) would have been sufficient to have detected all but one of the nine patients without retinopathy who had an impaired contrast sensitivity.

Discussion

All the patients had a Snellen acuity of 5/5 or better, corrected if necessary. Nevertheless, nine of the 22 without retinopathy and six of the 20 with retinopathy had contrast test scores more than 2 standard deviations below the norm. No comparable figures are available from previous studies, although Ghafour *et al.*[6] report a significant difference between normals and diabetic patients without retinopathy as well as those with. In neither the present study nor those previous to it was impairment in contrast sensitivity[6 28] or other visual function[30] related to observable retinal pathology (except when the pathology was gross[7]), possibly because the retinopathy is often very localised. The test we have described measures visual function within the central 1·5° of the visual field. If impaired function precedes clinically evident anatomical changes, it is likely that those patients whose contrast sensitivity was impaired may later show background retinopathy.

Despite its simplicity and the speed with which it could be administered our test was sensitive enough to show the expected decline in sensitivity with age[31–35] and to reveal an impaired sensitivity in certain diabetic patients.[6 7 28] There is a high test-retest reliability, perhaps because the forced choice procedure reduced variation due to changes in the subjects' strategy and criterion.[26 32 36] The test is inexpensive, portable, and easy to score, and it can examine contrast sensitivity in any orientational meridian. Although it can measure contrast threshold at only one spatial frequency, the frequency chosen is that at which the visual system is most sensitive[23] and which has been shown to discriminate diabetic patients from normal subjects.[6] The test is designed to be administered only to patients who have normal Snellen acuity, but this restriction is less of a disadvantage than it might seem, given that the test is useful in detecting deficits that are not measurable by other clinical methods.[37]

The authors thank J G Robson and I Nimmo-Smith for their advice, P Hall, G Plant and their colleagues in the EEG department at Addenbrookes Hospital, Cambridge, for trying out a preliminary version of the test, M Barrett for assistance with the contrast measurements, and C D Binnie for the use of computing resources.

NOTE. A new version of the test, using letters, is currently in preparation in collaboration with Dr J G Robson. Copies of this test, and of the test described here, can be obtained for a nominal charge by writing to the last-named author.

References

1 Bodis-Wollner I. Detection of visual defects using the contrast sensitivity function. *Int Ophthalmol Clin* 1980; **20:** 135–53.

2 Bodis-Wollner I. Visual acuity and contrast sensitivity in patients with cerebral lesions. *Science* 1972; **178:** 769–71.

3 Bodis-Wollner I, Diamond SP. The measurement of spatial contrast sensitivity in cases of blurred vision associated with cerebral lesions. *Brain* 1976; **99:** 695–710.

4 Paulsson LE, Stostrand J. Contrast sensitivity in the presence of a glare light: theoretical concepts and preliminary clinical studies. *Invest Ophthalmol Visual Sci* 1980; **19:** 401–6.

5 Hesse RF, Woo G. Vision through cataracts. *Invest Ophthalmol Visual Sci* 1978; **17:** 428–36.

6 Ghafour M, Foulds WS, Allan D, McClure F. Contrast sensitivity in diabetic subjects with and without retinopathy. *Br J Ophthalmol* 1982; **66:** 492–5.

7 Hyvärinen L, Laurinen P, Rovamo J. Contrast sensitivity in evaluation of visual impairment due to diabetes. *Acta Ophthalmol* 1983; **61:** 94–101.

8 Wolkstein M, Atkin A, Bodis-Wollner I. Contrast sensitivity in retinal disease. *Ophthalmology* 1980; **87:** 1140–9.

9 Shalka HW. Comparison of Snellen acuity, VER acuity and Arden grating scores in macular and optic nerve diseases. *Br J Ophthalmol* 1980; **64:** 24–9.

10 Sjostrand T. Contrast sensitivity in macular disease using a small-field and a large-field TV system. *Acta Ophthalmol (Kbh)* 1979; **57:** 832–46.

11 Arden GB, Jacobson JJ. A simple grating test for contrast sensitivity; preliminary results indicate value in screening for glaucoma. *Invest Ophthalmol Visual Sci* 1978; **17:** 23–32.

12 Atkin A, Wolkstein M, Bodis-Wollner I, Anders M, Kels B, Podos S. Interocular comparison of contrast sensitivities in glaucoma patients and suspects. *Br J Ophthalmol* 1980; **64:** 858–62.

13 Cooper RL, Constable IJ, Terrell A. Mass screening for glaucoma and other eye disease using the Arden grating test. *Aust J Ophthalmol* 1980; **8:** 131–7.

14 Editorial. Contrast sensitivity revisited. *Br J Ophthalmol* 1981; **65:** 513–4.

15 Singh H, Cooper RL, Alder VA, Crawford GJ, Terrell A, Constable IJ. The Arden grating acuity: effect of age and optical factors in the normal patient with prediction of the false negative in screening for glaucoma. *Br J Ophthalmol* 1981; **65:** 518–24.

16 Regan D, Silver R, Murray TG. Visual acuity and contrast sensitivity in multiple sclerosis: hidden visual loss. *Brain* 1977; **100:** 563–79.

17 Zanen A. Diminution de la sensibilité au contrast spatial et stéréoillusion de Pulrich chez des patients atteints de sclérose en plaques. *Bull Soc Belge Ophtalmol* 1982; **199–200:** 95–115.

18 Zimmern RL, Campbell FW, Wilkinson IM. Subtle disturbance of vision after optic neuritis elicited by studying contrast sensitivity. *J Neurol Neurosurg Psychiatry* 1972; **42:** 407–12.

19 Hess RF, Carney LG. Vision through an abnormal cornea: a pilot study of the relationship between visual loss from corneal dislocation, corneal edema, keratoconus and some allied corneal pathology. *Invest Ophthalmol Visual Sci* 1979; **18:** 476–83.

20 Bender MD, Bodis-Wollner I. Visual dysfunction in optic tract lesions. *Ann Neurol* 1978; **3:** 187–93.

21 Marron JA, Bailey IL. Visual factors and orientation-mobility performance. *Am J Optom Physiol Opt* 1982; **59:** 413–26.

22 Campbell FKW, Maffel I. Contrast and spatial frequency. *Sci Am* 1974; **231:** 106–14.

23 Campbell FKW, Robson JG. Application of Fourier analysis to the visibility of gratings. *J Physiol (Lond)* 1968; **197:** 551–6.

24 Editorial. Spatial contrast sensitivity. *Br J Ophthalmol* 1978; **62:** 197.

25 Arden GB. The importance of measuring contrast sensitivity in cases of visual disturbance. *Br J Ophthalmol* 1978; **62:** 198–209.

26 Vaegan, Halliday BL. A forced-choice test improves clinical contrast sensitivity testing. *Br J Ophthalmol* 1982; **66:** 477–91.

27 Arden GB. Visual loss in patients with normal visual acuity. *Trans Ophthalmol Soc UK* 1978; **98:** 219–31.

28 Hirsch J, Puklin JE. Reduced contrast sensitivity may precede clinically observable retinopathy in type I diabetes. In: Henkind P, ed. *Acta XXIV International Congress of Ophthalmology, S Francisco, 1982.* Philadelphia: Lippincott, 1983: 719–24.

29 National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979; **28:** 1039–57.

30 Kinnear PR, Aspinall PA, Lakowski R. The diabetic eye and colour vision. *Trans Ophthalmol Soc UK* 1972; **92:** 69–78.

31 Shalka HW. Effect of age on Arden grating acuity. *Br J Ophthalmol* 1980; **64:** 21–3.

32 Vaegen. The clinical value of printed contrast sensitivity tests. *J Physiol (Lond)* 1980; **300:** 76P.

33 Sekuler R, Hutman IP, Owsley CJ. Human aging and spatial vision. *Science* 1980; **209:** 1255–6.

34 Sekuler R, Hutman IP. Spatial vision and aging. Contrast sensitivity. *J Gerontol* 1980; **35:** 692–9.

35 Beazley LD, Illingworth DJ, John A, Greer DV. Contrast sensitivity in children and adults. *Br J Ophthalmol* 1980; **64:** 863–6.

36 Hutman LP, Sekuler R. Spatial vision and aging. Criterion effects. *J Gerontol* 1980; **35:** 700–6.

37 Arden GB. Visual loss in patients with normal visual acuity. *Trans Ophthalmol Soc UK* 1978; **98:** 219–23.

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Gas gangrene infection of the eyes and orbits

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SUMMARY The literature on *Clostridium perfringens* infections is reviewed up to 1983. An additional case is reported with bilateral clostridial infections of the eye and orbit. One eye followed the classical course of relentless panophthalmitis, amaurosis, and orbital cellulitis ending in enucleation. The second eye contained intracameral mud and gas bubbles that were removed by vitrectomy instrumentation. Subsequent removal of the toxic cataract resulted in a final aided visual acuity of 6/18, N8. This is the third report of a retained globe, and we believe the only known case where the patient was left with useful vision.

Clostridium perfringens is a ubiquitous Gram-positive bacillus found in soil and bowel flora. It is the most common of four clostridia species identified in cases of gas gangrene in man.[1] All species are obligate anaerobes and are usually saprophytic rather than pathogenic. *Clostridium perfringens* is a feared contaminant of limb injuries and may result in death due to the effects of its powerful exotoxins, which include lecithinase, phospholipase, neuraminidase, cytolysin, collegenase, and DNA-ase.[2]

Despite the potential frequency of contamination intraocular infection is rare. When the infection is established, however, the outcome has been loss of the globe in almost every case. Systemic toxicity has been reported rarely, perhaps because established panophthalmitis has been almost uniformly treated by surgical removal of the globe or orbital contents. Our recent experience from a case with bilateral ocular and orbital involvement confirms the sinister nature of such an infection but, for the first time, provides evidence that curative measures are now available.

Case report

A 38-year-old male construction worker struck a stick of gelignite with a pick while digging a trench on 28 August 1982. In the explosion that followed he suffered extensive superficial injuries to the face, arms, chest, and abdomen. He was admitted to a general hospital, where he was examined under anaesthesia, and his injuries were attended to.

Ocular findings. The right cornea and anterior chamber were intact. There was a scleral laceration over the superonasal area of the pars plana with vitreous prolapse. Pieces of stone were seen in the vitreous, and there was commotio retinae. An attempt was made to remove the foreign bodies with Sutherland forceps. This was unsuccessful, and the scleral wound was closed.

In the left eye there was a corneal perforation nasally with a tear in the underlying iris. Mud and other debris were present in the anterior chamber particularly in the inferior angle. The corneal wound was sutured with 10/0 monofilament nylon. After closure of the corneal wound two ports (nasal and temporal) were made inside the limbus, but it was not possible to clear the anterior chamber with Sutherland forceps. The facial wounds were cleared out, and subconjunctival injections of gentamycin and cephalosporin were given. Parenteral therapy was also started with these same antibiotics. The patient was transferred to the Royal Victorian Eye and Ear Hospital on 29 August 1982 and taken straight to the operating theatre.

Operative findings 29 August 1982. The right eye showed diffuse corneal oedema, and multiple granular particles of dirt were embedded in the stroma. There was a total hypopyon. A vitreous biopsy was taken through the pars plana (single port) with the Intra Ocular Cutter (IOC) Micro-Fine, Australia. The aspirate was greyish-brown and fluid

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in consistency. Filtered air was injected into the eye together with 8 μg of gentamycin. There was gross oedema of both lids with multiple embedded foreign bodies.

On the left side the lids were similarly swollen and impregnated with foreign materials. There were full thickness wounds in the superotemporal and inferotemporal regions that extended deep into the orbit. These tracks were filled with greyish pus and debris. They were irrigated and rubber drains were inserted. The left cornea was impregnated with small quartz and other particles of earth. There was an abscess around the perforation site and generalised corneal oedema. A small gas bubble was evident in the anterior chamber that contained mud, quartz particles, and hypopyon.

The anterior chamber was cleared through two limbal ports with the IOC. The mud was enmeshed in a dense fibrin layer all of which came away en masse from the anterior surface of the iris after infusion aspiration. Streptomycin (250 mg) was injected subconjunctivally.

At dressing on 30 August there was a purulent discharge from the right eye. The cornea was completely hazy. There was marked proptosis, external ophthalmoplegia, and no light perception. The left cornea was reasonably clear except for the area of infiltration around the original laceration, and, apart from some residual exudate around the pupil margin, the left anterior chamber was satisfactory. The antibiotic regimen was modified on receipt of the culture and sensitivity reports.

Enucleation of the right eye was performed on 30 August 1982. The operation was virtually bloodless. The resolution of signs was rapid, and a prosthesis was fitted three weeks later.

The postoperative course was marked by temperature spikes that subsided within the week and by leucopenia. The vision of the left eye improved from perception of light to counting fingers at 2 feet (60 cm). The cornea cleared except for scarring around the perforation site. There were anterior and posterior subcapsular lens opacities that progressed over the next two months. Repeated ultrasonography failed to show any evidence of an intraocular foreign body. A planned extracapsular cataract extraction was done on 22 November 1982. Convalescence on this occasion was uneventful.

The best recorded visual acuity on 10 February 1983 was 6/18 with +13·0/−2·25 axis 110° and N8 with a +3·0 addition. The fundus appeared normal. The limitation in distance acuity was due to the corneal scar that intruded on the pupil area nasally and to some thickening of the posterior lens capsule (Fig. 1).

Pathological findings. Gram-positive bacilli and polymorphs were identified in smears of material from both eyes, and *Clostridium perfringens* was cultured from each eye.

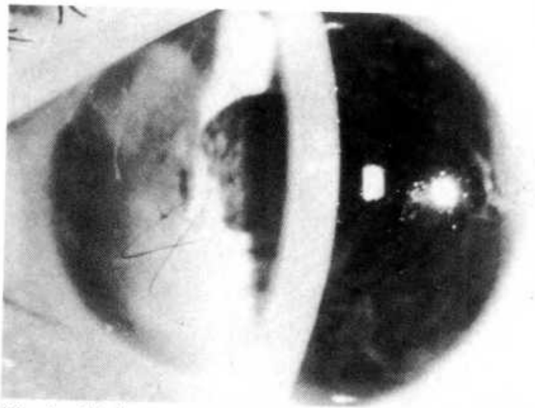

Fig. 1 *Slit-lamp photograph of the anterior segment of the left eye following extracapsular cataract extraction. Best acuity 6/18, N8.*

Histopathological examination of the enucleated right eye showed a panophthalmitis (Fig. 2). There was a heavy infiltrate of polymorphs in the anterior chamber, vitreous, subretinal space, choroid, and sclera. The retina was detached and partly necrotic. Very few Gram-positive bacilli were identified within the inflammatory exudate.

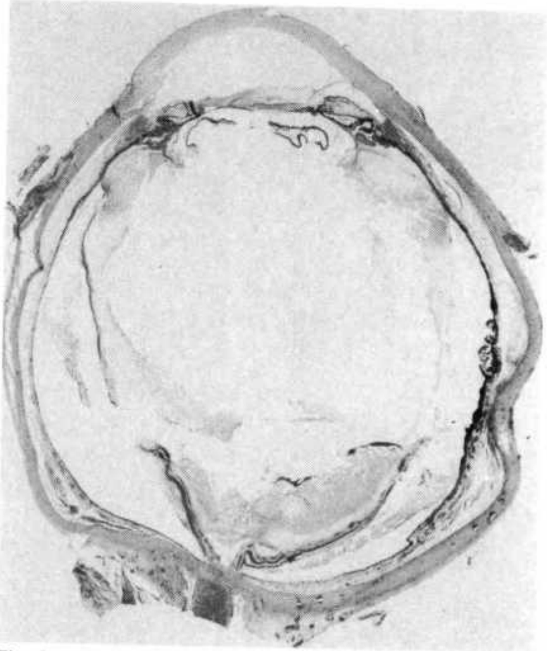

Fig. 2 *Photomicrograph of histological section of the enucleated right eye. The retina is totally detached, and there is an acute inflammatory exudate through all coats of the eye. (Haematoxylin and eosin, ×3).*

Discussion

SYNOPSIS OF PREVIOUS CASE REPORTS

The modern literature on gas gangrene of the eye was inaugurated by the French between 1904 and 1906.[3-6] More than 20 years later Frederick Ridley could cite only five case reports. In a brief but masterful paper he described a single additional case and defined the clinical hallmarks of this disease.[7] In 1936 Kluever and O'Brien[8] added another single case and, in reviewing the literature, referred to gangrenous dacryocystitis. They conducted extensive laboratory and animal experiments on the causative organism from their case. As early as 1938 it was noted by Sidney Walker that ocular infection by *Clostridium perfringens* did not carry the same risk of mortality as was associated with contaminated limb wounds, nor the same frequency of occurrence.[9]

The first instance of the use of antibiotics against clostridial ophthalmitis was contained in McGregor's report of the case of a maltster who presented with a five day history of severe pain in the right eye and grossly swollen lids.[10] Small incisions had been made in the outer third of both lids close to the orbital margins. Brown pus and bubbles were escaping from the wounds. The smell was foul. Sinus lavages were repeated over six weeks, then a radical antrostomy was performed. *Staphylococcus aureus* and Gram-positive bacilli with filamentous forms, some resembling spores, were isolated. The patient was treated with antigas-gangrene serum and sulphathiazole. Fundus examination showed optic atrophy only. There was no perception of light in the eye.

The use of penicillin was first reported by Capus in 1946[11] in an injury sustained after the explosion of a wooden military mine. The left eye at evisceration was found to contain an intraocular wooden foreign body and coffee coloured exudate, with gas of a characteristic odour. *Clostridium perfringens* was isolated and cultured from this material. The right eye, though injured superficially, was not similarly infected. The author noted that clostridial infection had occurred despite the early use of penicillin and sulphadiazine.

By 1951, when Kennedy and Vogel[12] added another civilian case of panophthalmitis due to *Clostridium perfringens*, the literature count had reached 28. In their patient the inexorable progress of the panophthalmitis was interrupted by intensive systemic penicillin therapy, though the eventual outcome for the eye was evisceration 60 hours after injury.

In 1955 Robert Leavelle[1] reviewed the literature and added three new cases of gas gangrene panophthalmitis. He briefly described a fourth case (not panophthalmitis)—a massive penetrating wound of the globe with confirmed *Clostridium perfringens* contamination. He detailed 24 authors who between them had described 53 cases since 1904. Four characteristics were common to every instance of gas gangrene panophthalmitis: infection followed a perforating wound of the globe; despite any and all measures undertaken the infection progressed and destroyed all visual function; the infected globe was either eviscerated or enucleated, or the entire orbit exenterated; postoperative recovery was essentially uneventful and complete. In all cases the course was fulminating regardless of the magnitude of the original injury. The three cases of Lutz were the exception in not following such a course.[13]

The diagnosis was suspected clinically in several cases but was not established by laboratory means in any case until more than 48 hours after injury. The end result was the same in all cases—complete disorganisation of the visual function and the final necessity for removal of the destroyed tissues by surgical means. Exenteration was necessary in two cases.

Clostridium perfringens conjunctivitis was first described as a clinical entity in 1963 by Henkind and Fedukowicz.[14] They reviewed the chronic unilateral *Clostridium perfringens* dacryocystitis followed by panopthalmitis as described by Beneditti,[15] the three cases of gas infection of the cornea after gunshot wounds to the eye described Pringle,[16] and the report of *Clostridium perfringens* contamination of the lashes without other evidence of infection.

Henkind and Fedukowicz reported on two patients,[14] both severely ill, who were faecally incontinent. Though the conjunctivitis was of the moderate exudative type, multiple small haemorrhages were present; the entire process was confined to the lower fornices and adjacent bulbar conjunctiva. A culture of *Clostridium perfringens* obtained from one patient was used to prepare a suspension for experimental purposes. Conjunctivitis occurred in one of three guinea-pigs into which the suspension had been injected. In 1970 Levitt and Stam[17] described the case of a young child injured by a splinter of wood. Therapy resulted in a retained globe with traumatic cataract and perception of light.

Bristow *et al.*[18] wrote from South Africa and contributed case 62 in 1971. This was the first recorded case in which hyperbaric oxygen was used as an adjuvant to therapy. They suggested that such therapy was indicated only when there is clinical evidence of extraocular extension of the gas gangrene. The disease was again cut short by evisceration. In the same issue of the journal case 63 was reported from England,[19] another fulminant panophthalmitis where a ring corneal abscess developed. These two papers evoked an editorial comment[20] which ended with the ominous statement that 'so far, no eye with proved gas gangrene panophthalmitis has ever been saved by antibiotic treatment alone.'

The contrast in systemic complications of general versus ocular clostridial infections was highlighted by a series of papers in 1973.[21-24] Involvement of the eye and orbit by gas gangrene was not discussed and has not been recorded in Australia previously.

In 1974 Frantz *et al.*[25] reported the only known case of *Clostridium perfringens* endophthalmitis produced by endogenous spread. The patient presented with simultaneous abdominal pain and loss of vision. At operation a perforated gangrenous gall bladder was found. The patient died and at necropsy both eyes were enucleated. The left eye was the seat of clostridial endophthalmitis. Detailed histological findings are given in the paper. After the single case of Kessler *et al.* in 1976 from Switzerland[26] the present report becomes the 67th to be presented.

COMMENTS

The literature of ophthalmic gas gangrene infections contains many single case reports that are depressingly repetitive in the final outcome, despite a variety of therapeutic initiatives. The classical course of this infection was succinctly summarised by Duke-Elder[27] (Table 1). He stated, 'In every case, usually within 24 hours after injury, a characteristic fulminating panophthalmitis develops with six distinctive clinical features, the recognition of which is important because of the necessity for urgent and radical treatment.'

Table 1 *Signs and symptoms of gas gangrene panophthalmitis*

1 Rapid onset with unusually severe pain
2 Brawny swelling of eyelids
3 Early rise in ocular tension
4 Blood of a thin coffee coloured discharge
5 Gas bubbles in anterior chamber
6 Rapid development of total amaurosis

One would be reluctant to add a further case report were it not for several noteworthy features, the foremost of which is a final visual acuity of 6/18, N8 in the left eye. Although survival of the globe with optic atrophy[10] and with dense cataract and perception of light[17] has been reported, this would seem to be the first case of bilateral infection in which the clinical course of the two eyes is vividly contrasted. The classical outcome on the right side, with amaurosis and hypopyon within 24 hours of sustaining an intravitreal foreign body, reinforces the justly feared devastation due to an established *Clostridium perfringens* infection. The left side, with a confirmed intracameral infection and gas bubble, was treated by vitrectomy instrumentation and antibiotics. The posterior pole was observed to be normal after the removal of the toxic cataract. The traumatic corneal leucoma and wrinkling of the posterior lens capsule were of sufficient degree to account for the reduction in the final visual acuity to 6/18, N8.

The involvement of both orbits showed differing clinical patterns—the right, secondary to the clostridial panophthalmitis; the left, by direct penetration of soil. The right orbit was not involved in the primary trauma, the site of penetration being several millimetres posterior to the limbus. Within 24

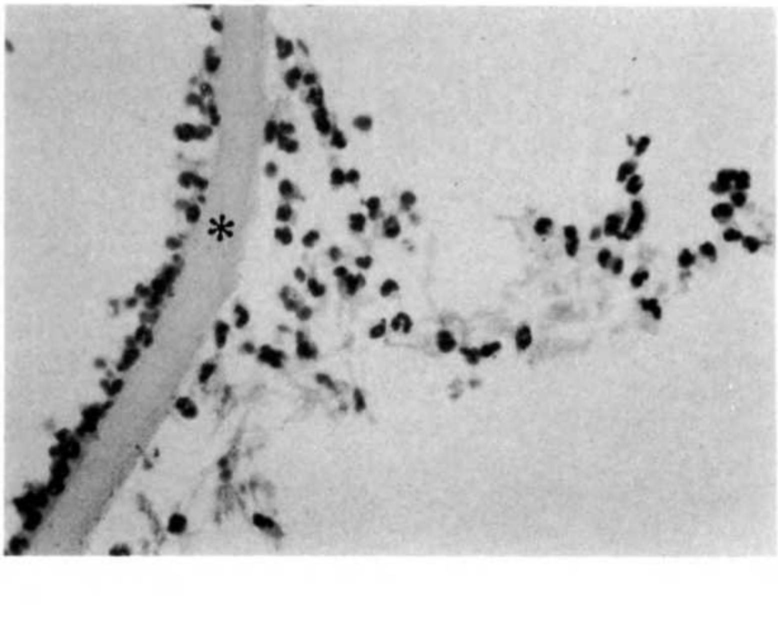

Fig. 3 *Histological section from the enucleated right eye. The lens capsule (asterisk) is enclosed on both sides by polymorphs. (Haematoxylin and eosin, ×243).*

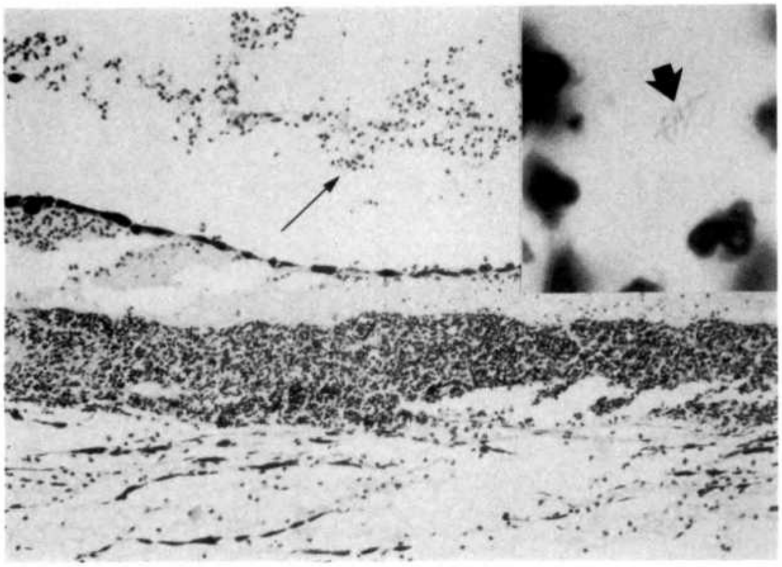

Fig. 4 *Photomicrograph of the choroid from the enucleated right eye. There is a heavy infiltrate of polymorphs in the choroid. There are moderate numbers of polymorphs in the subretinal space (long arrow). (Haematoxylin and eosin,* ×*61)* Inset: *Gram-positive bacilli (short arrow) are identified within the inflammatory exudate. (Gram stain, oil immersion,* ×*608).*

hours there were signs of orbital cellulitis with a marked proptosis accompanying the intraocular suppuration. The orbital cellulitis was almost certainly part of the panophthalmitis and not the result of a separate inoculation. Histopathological examination of the enucleated eye confirmed a panophthalmitis with only occasional identifiable microorganisms. This is consistent with previous reports,[1 18] where scanty organisms were found in the affected globe despite severe disruption of the contents. These findings highlight the powerful effect of the exotoxins produced by *Clostridium perfringens*, which not only cause rapid destruction of the lens, as seen in the present case (Fig. 3), retina, and choroid (Fig. 4), but also affect the extraocular tissues.

The degree of proptosis of the right globe was marked. In contrast there was minimal swelling of the left orbit, despite deep tracts into it, contaminated by soil containing *Clostridium perfringens*. The difference in the degree of tissue swelling was probably attributable to the effective decompression of the left orbital septum by the explosive penetrations.

With regard to management the significant factor that differs from all earlier reports is the use of vitrectomy instrumentation. Because of early opacification in the media of the right eye its application was limited to a vitreous biopsy on that side. However, in the left eye the removal of the fibrin-enmeshed mud from the iris and inferior angle was dramatic both in execution and effect. Culture of this material confirmed the presence of *Clostridium perfringens*, and the gas bubble attested to its activity. While the useful visual outcome may be attributed to the removal of the mud and inoculum of organisms from the anterior chamber, one must be cautious in according the success entirely to surgical intervention.

Clostridium perfringens requires specific conditions for fulminant growth and the production of exotoxins. Von Sallman,[28] using an experimental model to test antibiotic sensitivities, could produce clostridial panophthalmitis only by inoculation of organisms deep into the nucleus of the lens. After six hours penicillin could not arrest the bacterial growth. By contrast *Staphylococcus aureus* and *Streptococcus pneumoniae* would reliably induce panophthalmitis after inoculation into the anterior chamber after only a few superficial scratches were made on the anterior surface of the lens. Von Sallman's work highlighted the importance of the low redox potential necessary for the growth of *Clostridium perfringens*. In the eye this is found in the avascular tissue of the lens and vitreous. Owing to the vascularity of the iris the anterior chamber has a higher oxygen level than the vitreous or lens and is less favourable to the growth of anaerobes. With regard to the case presented here the successful culture of the organisms some 24 hours after trauma, and the production of the gas bubble, confirms that the anterior chamber will support the growth of *Clostridium perfringens* in the presence of debris.

The successful outcome on the left side invites speculation that early vitrectomy with removal of all foreign material may have altered the outcome for the right eye. While simple removal (by magnet) of a foreign body, even within six hours of trauma, has not prevented panophthalmitis,[29] the early removal of the avascular vitreous would theoretically reduce the size of the inoculum, remove the majority of the avascular tissue, and irrigate the vitreous cavity with oxygenated fluid.

The major obstacle to implementation of such management is the fact that microbiological confirmation may not be available for 24 hours or more. Simple foreign body removal is all that is warranted in many cases of penetrating injuries, and surgeons are rightly loath to perform acute vitrectomy unless certain of its benefit. However, the catastrophic outcome of established clostridial panophthalmitis brooks no delay for traditional microbiological culture methods. Therefore, cases of military and civilian injuries should be regarded as being at just as high a risk of clostridial infection in the eye as in the limbs or abdomen. They should be assessed for the potential benefit of debridement of avascular and necrotic tissue, which, in the eye, would involve total vitrectomy and also lensectomy if the lens were involved.

References

1 Leavelle RB. Gas gangrene panophthalmitis. *Arch Ophthalmol* 1955; **53:** 634–42.
2 McDonel JL. Clostridium perfringens toxins (Type A, B, C, D and E). *Pharmacol Ther (B)* 1980; **10:** 617–55.
3 Chaillous J. Infection traumatique du globe oculaire par un microbe anaerobic (Bacillus perfringens). *Rec Ophtalmol* 1904; **26:** 678–80.
4 Chaillous J. Deux cas d'infection traumatique due globe oculaire par un microbe anaerobic (Bacillus perfringens). *Ann Oculist (Paris)* 1905; **134:** 115.
5 Darier A. Panophtalmie et Bacillus perfringens. *Clinique Ophtalmologique* 1905; **11:** 266.
6 Darier A. Panophtalmie gazeuse et bacillus perfringens. *Clinique Ophtalmologique* 1906; **12:** 227–9.
7 Ridley F. Gas gangrene panophthalmitis. *Trans Ophthalmol Soc UK* 1929; **49:** 221–5.
8 Kluever HC, O'Brien CS. Panophthalmitis due to Clostridium welchii. *Arch Ophthalmol* 1936; **15:** 1088–93.
9 Walker S. Prognosis of Bacillus welchii panophthalmitis. *Arch Ophthalmol* 1938; **19:** 406–8.
10 McGregor IS. Orbital cellulitis from gas producing organisms. *Br Med J* 1942; **i:** 292–3.
11 Capus B. Clostridium welchii panophthalmitis. Report of a case. *Arch Ophthalmol* 1946; **36:** 226–8.
12 Kennedy RJ, Vogel AW. Intraocular infection with the gas-forming bacillus Clostridium welchii. *Arch Ophthalmol* 1951; **45:** 528–30.
13 Lutz A. Über einige Falle von ektogener Panophthalmie (infektionen mit Pneumococcus subtilis und anaerobionten). *Klin Monatsbl Augenheilkd* 1910; **48:** 31.
14 Henkind P, Fedukowicz H. Clostridium welchii conjunctivitis. *Arch Ophthalmol* 1963; **70:** 791–5.
15 Benedetti A. Panoftalmite a bacillo 'perfringens.' *Clin Oculist (Palermo)* 1970; **8:** 3013.
16 Pringle JA. Three cases of gas infection of the cornea following gunshot wounds to the eye. *Br J Ophthalmol* 1919; **3:** 110.
17 Levitt JM, Stam J. Clostridial perfringens panophthalmitis. *Arch Ophthalmol* 1970; **84:** 227–8.
18 Bristow JH, Kassar B, Sevel D. Gas gangrene panophthalmitis treated with hyperbaric oxygen. *Br J Ophthalmol* 1971; **55:** 139–42.
19 Bhargava SK, Chopdar A. Gas gangrene panophthalmitis. *Br J Ophthalmol* 1971; **55:** 136–8.
20 Anonymous. Gas gangrene of the eye. (Editorial). *Br Med J* 1971; **ii:** 419–20.
21 Unsworth IP. Gas gangrene in New South Wales. *Med J Aust* 1973; **i:** 1077–80.
22 Shaw J, Vellar ID, Vellar D. Clostridial (gas gangrene) infection in a general hospital. *Med J Aust* 1973; **i:** 1080–7.
23 McKinnon D, McDonald P. Gas gangrene—a ten-year survey from the Royal Adelaide Hospital. *Med J Aust* 1973; **i:** 1087–90.
24 Deveridge RJ, Unsworth IP. Gas gangrene. *Med J Aust* 1973; **i:** 1106–9.
25 Frantz JF, Lemp MA, Font RL, Stone R, Eisner E. Acute endogenous panophthalmitis caused by Clostridium perfringens. *Am J Ophthalmol* 1974; **78:** 295–303.
26 Kessler S, Schmid E, Pagon S. Panophthalmie durch Gasbranderreger. *Klin Monatsbl Augenheilkd* 1976; **168:** 134–7.
27 Duke-Elder S. *System of ophthalmology*. London: Kimpton, 1972; **14:** 405–10.
28 von Sallman L. Penicillin and sulfadiazine in the treatment of experimental intraocular infections with Staphylococcus aureus and Clostridium welchii. *Arch Ophthalmol* 1944; **31:** 54–63.
29 Walsh T. Clostridial ocular infections. Case report of gas gangrene panophthalmitis. *Br J Ophthalmol* 1965; **49:** 472–7.

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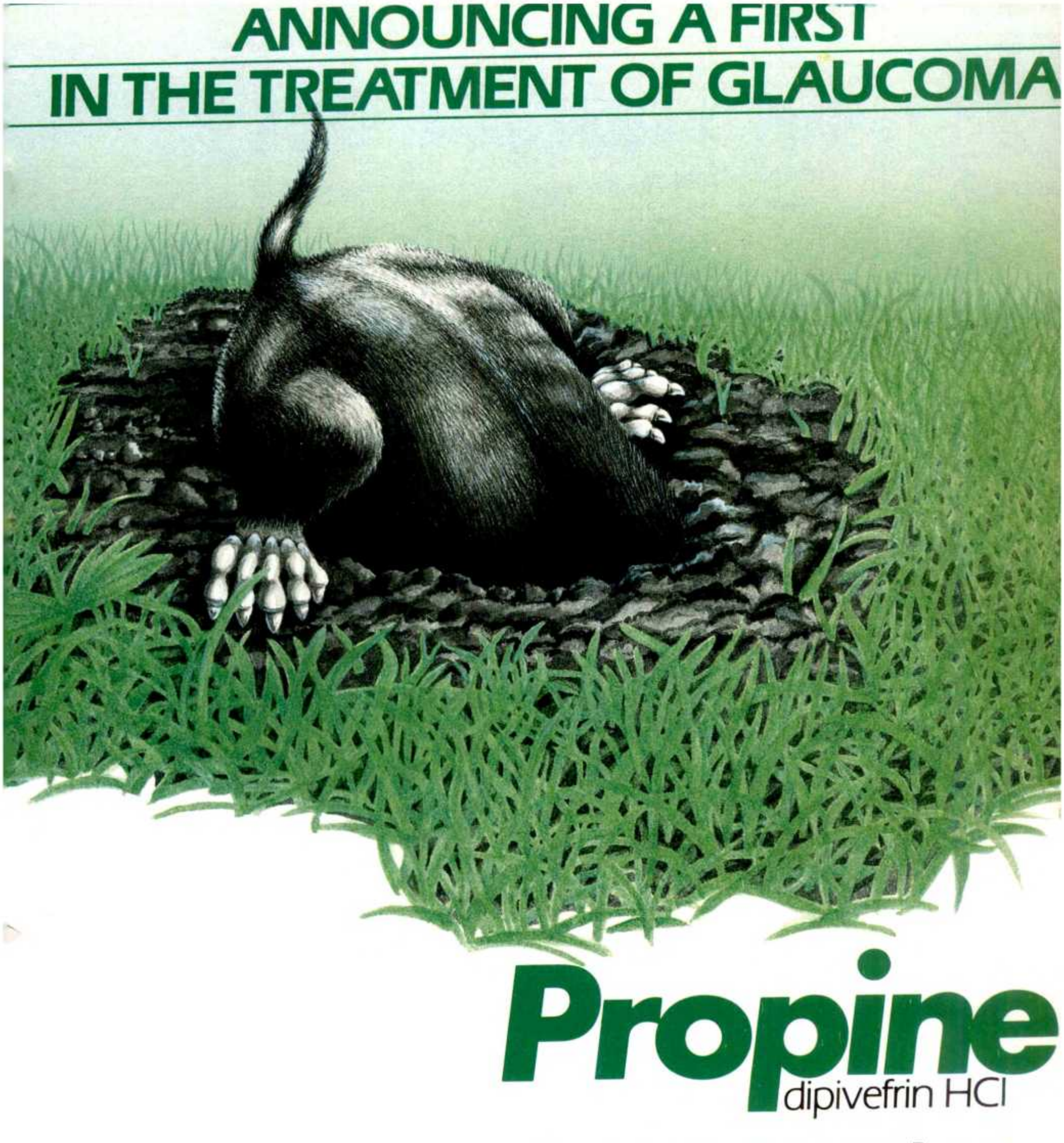

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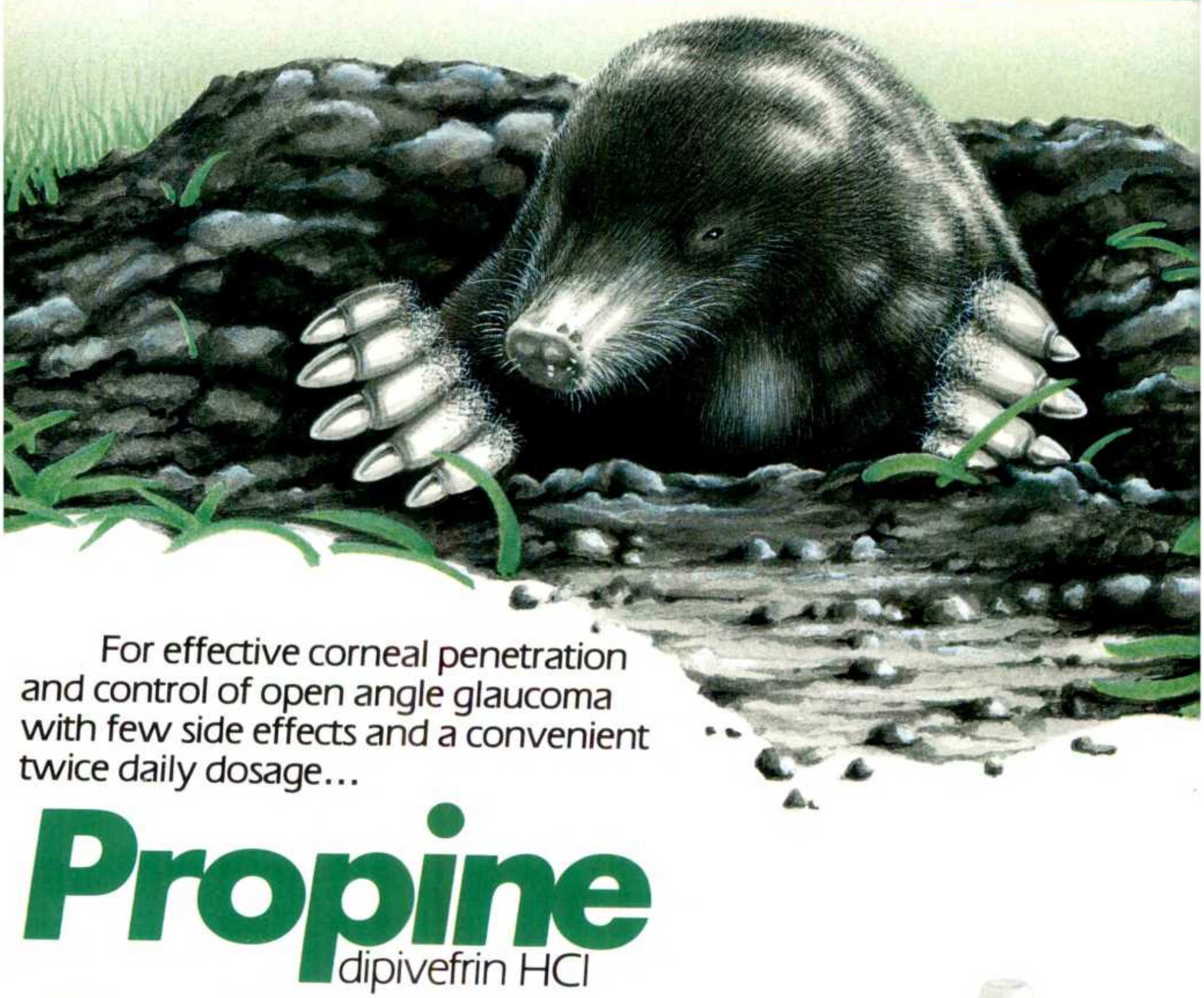

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Experimental ocular siderosis after extrabulbar administration of iron

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SUMMARY The authors studied the penetration of iron administered extrabulbarly into the ocular tissues of rabbits. It was found that iron passes from the orbit into the eyeball and accumulates in considerable quantities in the sclera, choroid, retina, ciliary body, and even in the vitreous and corneal epithelium. However, light microscopy failed to show any damage to the ocular tissues. The mechanism by which iron penetrates into the eyeball is discussed, and comparison is made between changes in the tissues, which characterise siderosis produced by an intrabulbar iron foreign body, and those in which an extrabulbar foreign body is involved.

Changes which are produced by intrabulbar iron splinters are well known to every ophthalmologist, but there is less knowledge of changes caused by iron that has penetrated into the orbit in the vicinity of the eyeball. Most clinical reports point to the absence of any harmful action of such foreign bodies.[1] There is, however, a report of a case of siderosis cataract produced by an orbital foreign body adhering to the eyeball.[2] The objective of the present study was to find out to what extent, if at all, iron can penetrate from the orbit into the eyeball, and especially into the retina.

Material and methods

Twenty four eyes of 12 albino rabbits weighing 2·5–3 kg were used for the study. In each animal the bulbar conjunctiva of both eyes was incised in the inferonasal quadrant, and after exposing the sclera 15 mg of iron in powder form was placed in the equator region. The conjunctiva was closed with a continuous suture, which was removed on the seventh day. In the fifth, ninth, and twelfth month after the administration of iron the eyeballs were taken for histological examination after systemic perfusion of the blood vessels to prevent distortion of tissues in the fixation process. The perfusion was carried out as follows: after exposing the heart we introduced a metal cannula into the ascending aorta through the left heart ventricle. The cannula was connected to a transfusion apparatus with 1000 ml of a perfusion liquid containing 2% paraformaldehyde and 2·5% glutaraldehyde. The liquid was introduced at a pressure of 90–100 mmHg. The eyeballs were collected 15 min after the cessation of the perfusion and were fixed according to the Szent-Györgyi technique. Histological sections were stained with haematoxylin and eosin. The Prussian blue reaction to Fe^{3+} and the Turnbull blue reaction to Fe^{2+} were also applied.[3] Both methods of detecting iron were modified to eliminate staining of

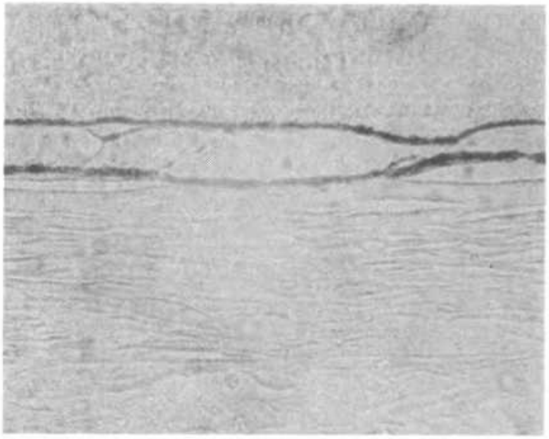

Fig. 1 *The sclera, choroid, and retina of a rabbit in which no iron was found. There is no staining of the individual morphological elements. The darker stain of the pigment epithelium and of part of the choroid is due to the presence of natural pigments. (Prussian blue reaction, ×150).*

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the background (nuclei and cytoplasm), so that the blue staining appeared only in those parts of the tissues which contained iron. For this reason the preparations of tissues free from iron remained unstained (Fig. 1). Since only slight changes were found in the eyes of the two rabbits killed in the fifth month, the eyeballs of the remaining 10 rabbits were collected in the ninth and twelfth months, from five animals at a time.

Results

The results of histological examination showed that iron placed in the orbit near the sclera penetrated inside the eyeball, and that it was a very slow process. Five months after the administration of iron its deposition could be observed only in the superficial layers of the sclera, so that not more than one third of the thickness of the tissue was involved (Fig. 2). Small amounts of iron were also found in the subconjunctival tissue away from the site of the introduction of the iron powder. This penetration of iron seemed to favour the anterior direction, and traces of the metal were also observed under the conjunctiva in the limbus. In other parts of the eye no evidence of the presence of iron could be found.

After nine and 12 months the penetration of iron into the eyeball was much more pronounced. In these experimental groups the histological findings were similar, though the penetration of iron into the retina, choroid, and ciliary body was usually slightly stronger after 12 months than after nine months. However, these differences were by no means significant. At the same time considerable differences in the penetration process were seen in the individual animals. For these reasons, and because it was not possible to distinguish changes characteristic of either time period, both experimental groups are discussed jointly.

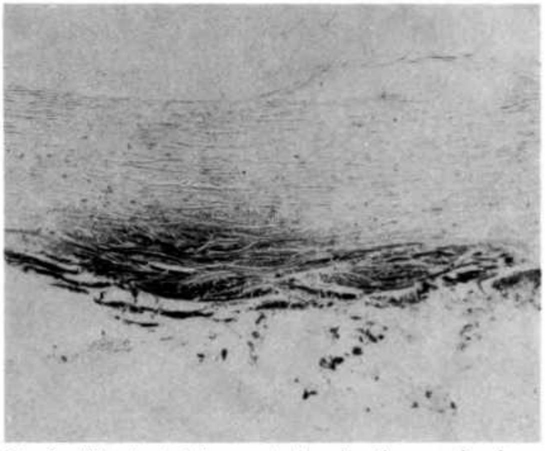

Fig. 2 *Histological changes in the sclera five months after administration of iron. There is diffuse staining of the external one-third of the tissue. (Prussian blue reaction, ×112).*

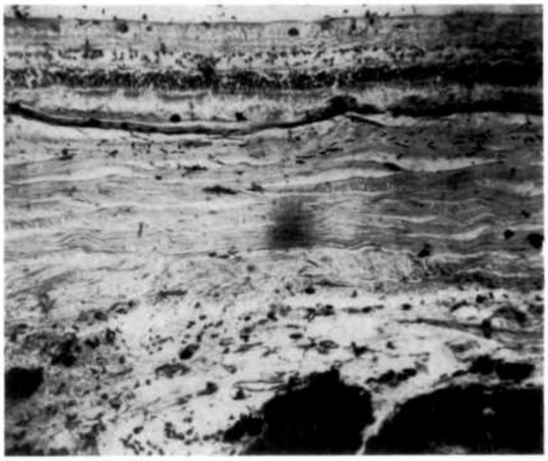

Fig. 3 *Histological appearance of the retina, choroid, and sclera 12 months after administration of iron. There is diffuse and granular staining of all layers of the eyeball wall. (Prussian blue reaction, ×150).*

Preparations stained with the use of the reactions to Fe^{2+} and Fe^{3+} showed that iron present in the tissues had produced two forms of staining: either minute and strongly stained granular agglomerations, or diffuse staining of whole tissues or of their parts. In the vicinity of the deposited iron powder the penetration of the metal through the whole sclera appeared in the form of both diffuse and granular staining (Fig. 3). In the parts of the sclera furthest away from the implantation site changes were observed in the external layers of the tissue, and the staining was diffuse. As far as the choroid is concerned, iron could be seen primarily in the vessel walls. The site of an especially intensive accumulation of iron was the pigment epithelium of the retina (Fig. 3). Bruch's membrane took a weak stain and could hardly be seen in the preparations (Fig. 4).

Iron usually pervaded the whole retina. This appeared as diffuse staining of all its layers. The most intensive staining was present in the external and internal nuclear layer (Fig. 3). The neuroepithelium and the nerve fibre layer showed a weaker stain, but the walls of the retinal vessels and the internal limiting membrane stained fairly strongly (Fig. 4). Strongly stained agglomerations of iron were also seen scattered in all layers of the retina—on its surface, and in the adjacent part of the vitreous (Fig. 4). Occasionally a detachment of the vitreous was observed. Its surface showed a fairly strong staining.

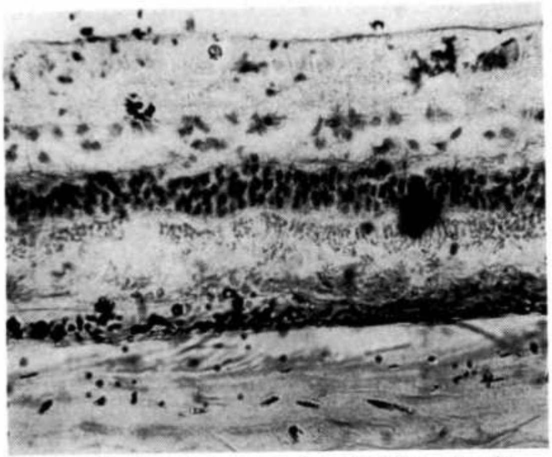

Fig. 4 *Histological changes in the retina 12 months after administration of iron. There is staining of all layers of the retina and especially strong reaction in the pigment epithelium, internal and external nuclear layer, and internal limiting membrane. There is staining of iron agglomerations. (Turnbull blue reaction, ×264).*

Of the other parts of the eye, the ciliary body, and above all its processes, were observed to have accumulated iron, mostly in the ciliary epithelium. The stroma of the ciliary body showed a less intense staining but contained agglomerations of iron (Fig. 5). Small traces of iron were found in the iris and anterior chamber angle. A diffuse staining was present in the corneal epithelium, but in other parts of the cornea iron could not be detected.

The blue stain owing to the presence of iron, was more intense in the Fe^{3+} reaction than in the Fe^{2+} reaction. In preparations stained with haematoxylin and eosin no distinct changes were found that could point to damage sustained by the ocular tissues. The only change was a spreading apart of the collagen fibres of the sclera in the sites of iron accumulation.

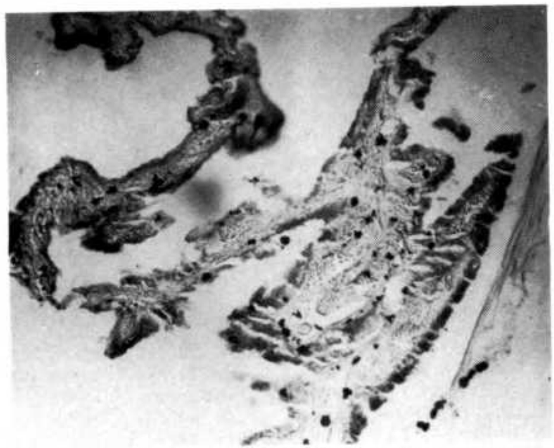

Fig. 5 *Histological appearance of the ciliary processes, 12 months after administration of iron. There is strong diffuse staining of the ciliary epithelium and less intense staining of the stroma, in which iron agglomerations are visible. (Prussian blue reaction, ×264).*

Discussion

The results of our study indicate that iron, when administered extrabulbarly, penetrates to a large extent into the eyeball and accumulates in the ocular tissues, among others in the retina. Two forms of iron staining were seen in the tissues: the diffuse and the granular form. It seems that the diffuse stain results from the penetration of iron through successive layers of the eyeball wall, while the granular form of iron is probably transported to the tissues by migrating cells.

The histological changes observed in this experiment are considerably different from those in siderosis caused by an intrabulbar foreign body. In the latter case iron is deposited above all in the ciliary epithelium, iris, and pigment epithelium of the retina, and in the internal layers of the retina in man and monkeys,[4-7] or in the external layers of the retina of the rabbit.[4 7] Smaller amounts of iron were found in the epithelium and fibres of the lens and in the epithelium, stroma, and endothelium of the cornea.[4 8] No accumulation of the metal could be found in the choroid or sclera.[4 5 7] The changes were accompanied by extensive destruction and atrophy of the retina, while there was basically no damage to the iris, ciliary body, or cornea.[4 7]

Two fundamental differences in the histological picture were found by us after extrabulbar administration of iron, as compared with the changes observed by other authors with regard to intrabulbar iron foreign bodies. First, iron accumulated in the sclera, choroid, pigment epithelium of the retina, epithelium and stroma of the ciliary body, and in the corneal epithelium. However, no deposition of iron was detected in the iris or in the stroma and endothelium of the cornea. Second, there was no visible damage to the retina, as evidenced by preparations stained with haematoxylin and eosin. The above differences were probably linked with the rate at which, and the route by which, iron penetrated into the individual ocular tissues. The presence of an intrabulbar foreign body results in a massive and violent release of iron ions into the vitreous and from there into the retina. Some of the ions are bound in the tissues by iron binding substances, for example, apoferritin. It is thought that the remaining free ions, having undergone a redox reaction with the participation of ascorbic acid, contribute to the formation of free radicals $OH^{\cdot}$ and $OH_2^{\cdot -}$ These radicals depolymerise hyaluronic acid of the vitreous, reduce the content of non-saturated fatty acids, and oxidise lipids to lipoperoxides in the retina.[9 11 12] This results in damage to the retina because of inactivation of enzymes containing sulphhydryl groups, and in disintegration of amino acids and proteins. It was also found that lipoperoxides reduce the respiratory function of the retina and inhibit the regeneration of rhodopsin.[11] Iron ions also form stable complexes with sulphhydryl groups and imidazole proteins, which again results in inactivation of enzymes.[13]

Of the large quantity of iron ions released from an intrabulbar foreign body, only a small percentage can be removed by iron binding systems, for example, by ferritin, in the retina. The remaining free iron ions, acting through the processes described above, cause considerable damage to the retina.

A different situation arises with an iron foreign body situated outside the eyeball. The penetration of iron ions into the retina is very slow, and only a small number of ions can invade the eye at a given moment. It also seems that not all iron ions that have crossed the sclera reach the retina. Some of them can be conveyed to the anterior chamber via the suprachoroidal space. This supposition is strengthened by the finding that iron easily penetrates from the anterior chamber into the suprachoroidal space through the anterior chamber angle, even in initial stages of siderosis.[8] Bruch's membrane is probably another barrier to the penetration of iron.[1 5] Apart from that, a quantity of the metal can be bound in the sclera and choroid. All these factors may have contributed to the observation that only a small amount of iron, and at a slow rate, was able to infiltrate the retina. In this situation the iron binding properties of the retina could prove adequate to prevent the appearance of histologically detectable changes. However, the question remains open whether constant infiltration of iron for a period longer than 12 months will still be successfully counteracted by this defence system of the retina.

The penetration of iron from the orbit into the eyeball has recently been the subject of other experimental studies. Sinovich and Gudkova[14] found accumulation of iron in the retina and choroid of rats but failed to observe morphological changes in these tissues. Our previous work[15] showed that the presence of an iron foreign body in the orbit results in a considerable increase of iron concentration in the aqueous of rabbits. Burch and Albert[1] implanted iron splinters into the orbit and sclera of rabbits and observed an accumulation of the metal mainly in the sclera, choroid, and ciliary body, and only occasionally in the retina. On the other hand they frequently found local atrophy of the retina and choroid in the site of the foreign body. According to the same authors the typical site of the accumulation of iron that has penetrated from the orbit are the tissues situated at the junction of the sclera and choroid. In our study accumulation of iron was also seen in the retina, and even in the vitreous, in almost every animal. However, it should be borne in mind that our application of iron in the form of powder may have facilitated the penetration of the metal into the eyeball. Interestingly enough, we did not observe particularly strong reactions to iron in the tissues situated at the boundary between the sclera and choroid. It seems that such changes can be a transitional stage during the migration of iron into the eye. Since the penetration of iron in our experiment was faster than that observed by Burch and Albert, the infiltration of the metal at the junction of the sclera and choroid might have occurred between the fifth and ninth months of the experiment and therefore might have remained unnoticed by us.

The results of the present study speak in favour of the removal of iron splinters from the orbit, as it can be supposed that constant penetration of iron for a period longer than that observed in our experiment can lead to siderosis of the retina and, by that, to its damage.

References

1 Burch PG, Albert DM. Transscleral ocular siderosis. *Am J Ophthalmol* 1977; **84:** 90–7.

2 Sironi L. Siderotic cataract due to metallic splinter adhering to lateral wall of orbit without penetrating eyeball. *Boll Oculist* 1942; **21:** 585.

3 Gabe M. *Histological techniques.* Paris: Masson, 1976.

4 Declercq SS, Meredith PCA, Rosenthal AR. Experimental siderosis in the rabbit. *Arch Ophthalmol* 1977; **95:** 1051–8.

5 Masciulli L, Anderson DR, Charles S. Experimental ocular siderosis in the squirrel monkey. *Am J Ophthalmol* 1972; **74:** 638–61.

6 Vogel M. Morphologie der Metallosen. In: Neubauer H, Rüssmann W, Kilp H, eds. *Intraokulare Fremdkörper und Metallose.* München: Bergmann, 1977: 9–15.

7 Wise JB. Treatment of experimental siderosis bulbi, vitreous hemorrhage and corneal bloodstaining with deferoxamin. *Arch Ophthalmol* 1966; **75:** 698–707.

8 Appel J, Barishak YR. Histopathological changes in siderosis bulbi. *Ophthalmologica* 1978; **176:** 205–10.

9 Hofmann H, Khan MAH, Schmut O. Der Einfluss von Katalase und Superperoxydoismutase auf die Viskositätsänderung von Hyaluronsäurelösungen aus Rinderglaskörpern nach Zusatz von Eisenionen. *Klin Monatsbl Augenheilkd* 1983; **182:** 214–7.

10 Schmut O, Hofmann H. Verflüssigung des Glaskörpers/Mechanismus der Glaskörperverflüssigung. In: Neubauer H, Rüssmann W, Kilp H, eds. *Intraokulare Fremdkörper und Metallose.* München: Bergmann, 1977: 73–7.

11 Hiramitsu T, Majima T, Hasegawa Y, Hirata K. Formation of lipoperoxide in the retina in ocular siderosis. In: Neubauer H, Rüssmann W, Kilp H, eds. *Intraokulare Fremdkörper und Metallose.* München: Bergmann, 1977: 89–92.

12 Weiss H, Graf A. Über die Schädigung des retinalen Fettsäurenmusters nach intravitrealer Eiseninjektion. *Albrecht von Graefes Arch Klin Ophthalmol* 1975; **197:** 293–8.

13 Rüssmann W. Biochemie der Metallosen. In: Neubauer H, Rüssmann W, Kilp H, eds. *Intraokulare Fremdkörper und Metallose.* München: Bergmann, 1977: 45–53.
14 Sinovich VA, Gudkova EV. The effect of foreign metal bodies in the orbit on the eyeball coats. *Vestn Oftalmol* 1969; **82:** 10–3.
15 Gerkowicz K, Prost M. Experimental investigations on the penetration into the eyeball of iron administered intraorbitally. *Ophthalmologica* 1984; **188:** 239–42.

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Book reviews

Clinical Ophthalmology. By JACK J KANSKI. Pp. 340. £49·50. Butterworth: Sevenoaks, Kent. 1984.

This book is intended for the trainee ophthalmologist and covers the whole field of ophthalmology. There are 17 separate chapters; curiously the page numbers are not continuous but each chapter has its own numbering, so that 7.11 means page 11 in chapter 7.

Colour illustration throughout makes this a very valuable contribution to postgraduate textbooks. The tables, coloured diagrams, and clinical photographs are all of a very high standard, and it is a pleasure to see the publishers careful attention to page design. Clear headings make for easy reference and location of information, which will aid examination candidates in particular.

There are a few imbalances in the depth at which particular subjects are treated. Some receive detailed and definitive description, other equally common conditions receive relatively brief treatment. However, this balance is almost impossible to achieve in a textbook as comprehensive as this one, and the author has in general done well in organising the relative importance of topics. Some attention to the index will be required for any future editions, for it often misses all the text references. Again, back to the unusual page numbering, it might aid the index to revert to the conventional page numbering. Although it is perfectly possible for readers to refer to other more detailed textbooks on particular topics, it would be helpful to have enlarged sections on special investigation techniques. For example, computerised tomography receives only a quarter page description, whereas its importance in the investigation of intracranial and orbital disease has been enormous.

All in all this is an excellent and superbly illustrated textbook, a pleasure to read, and highly recommended for trainee ophthalmologists and more senior ophthalmologists for ready reference. JAMES L KENNERLEY BANKES

Extracapsular Cataract Extraction. By JARED M. EMERY AND DAVID J. MCINTYRE. Pp. 418. No price given. St Louis, Missouri: Mosby. 1983.

Though primarily a description of technique by the two main authors, this book includes other aspects of management such as advice given in print before surgery and the precise details of what is expected of the patient postoperatively.

The descriptions of the two methods of extracapsular extraction are set out in minute detail. Nothing is taken for granted, and no item is too small to escape inclusion. A colour atlas of the steps in the surgical procedure of cataract extraction and lens implantation consolidates the detailed discussion. In addition there are chapters on Kelman phacoemulsification, the management of postoperative complications, and statistics of visual results.

There seems little doubt that the posterior chamber implant is here to stay and it will eventually supersede the iris clip. The visual results are so rapidly acquired and are so similar to the intact eye that the effort needed to produce uncomplicated results is well worth while. The size of this book and the obsession with minutiae are a measure of the degree of effort necessary to perform in series this 'miracle' of modern surgery. The book is a must for the practising ophthalmic surgeon who wishes to be abreast of the times.

STEPHEN MILLER

Therapeutic Systems. 2nd edn. By KLAUS HEILMAN. Pp. 148. DM 28. Georg Thieme: Stuttgart, New York. 1983.

In this book the author, a professor of ophthalmology in Munich, covers the whole field of these relatively new drug delivery systems which are used in many different parts of the body. The theoretical advantages of such systems are numerous. A drug can be delivered to the target organ over a fixed duration in predetermined and constant amounts of unit time. This enables a smaller dose to be given. Side effects are therefore reduced, with improvement in drug safety. Patient compliance is also improved, and this is of especial value in conditions requiring chronic administration. These systems permit the use of agents which have a short half life or are normally too toxic; plasma drug levels are kept constant.

The chief ocular therapeutic system, the Ocusert, is described at length. This was the first such system to be used clinically. Though tried in bacterial, viral, and trachomatous conditions, the only available model is the Ocusert Pilo 20 and 40 releasing 20 µg and 40 µg/hour pilocarpine respectively. The advantages claimed are that less drug is delivered over a seven-day period than the equivalent in drops, which leads to a more constant aqueous level of drug, with a reduction of side effects such as miosis and ciliary spasm. If employed in chronic closed-angle glaucoma the depth of the anterior chamber is not reduced so much with Ocusert as drops. It is not obvious from reading this book why, after the initial enthusiasm some 10 years ago, Ocusert Pilo is not employed in any quantity in the UK, though brief mention is made of cost benefit in a chapter at the end of the book.

Other systems described include transdermal, oral, contraceptive, and the osmotic pump. The oral system (Oros) can deliver acetazolamide with, it is claimed, fewer side effects. The drug is released through a hole drilled by laser in the membrane.

This book, which will be of limited interest to ophthalmologists, gives one an insight into developments in drug administration. As stated in the foreword, apart from the manufacture of new drugs there is still a need to look at the safer use of existing agents. S. J. CREWS

Augenheilkunde in Klinik und Praxis. Vol. 3, Part 1. By H. VON J. FRANCOIS AND F. HOLLWICH. Pp. 582. DM 486. Georg Thieme Verlag: Stuttgart. 1983.

This really is a magnificent book and it is hard to avoid superlatives. It has all the excellence of its predecessors. The volume is in effect a combination of three books with contributions from eight authors—all of them professors.

The first section is devoted to disorders of eye movement and there are chapters on the diagnosis and therapy of squint by Hugonnier and Magnard, on squints in children by Otto, on amblyopia also by Otto, and on nystagmus by Kommerell. This is followed by a large section on the retina with contributions by Henkes, Deutmann, and Archer. Finally there are two small chapters on glaucoma-related subjects—gonioscopy and secondary glaucoma, both by Slezak.

The illustrations throughout are of the highest quality, and each chapter is followed by a comprehensive list of references. It is difficult in a book of such uniformly high standard to single out any particular aspect that requires special mention over the rest, equally difficult to find any fault. The contributions on squint and on retinal disease can be classed as definitive studies, and the only criticism is that the mixture is almost too rich, for we are presented under one cover with three books that could achieve great success independently.

The editors are to be congratulated on this contribution to ophthalmic teaching, and the German-speaking ophthalmologists for whom this book is written are to be envied. We look forward eagerly to part 2 and to volume 2 in the series.

T. J. FFYTCHE

The Eye and its Disorders. 2nd Ed. By PATRICK D. TREVOR-ROPER and PETER V. CURRAN. Pp. 628. £45·00. Blackwell Scientific Publications: Oxford, 1984.

This is a beautifully written preamble to ophthalmology. Nowhere in ophthalmology, or indeed in other scientific textbooks, will you find such exquisite English and beautifully constructed sentences. It is a delight to read, and sets out to be a guide for the candidate for the diploma in ophthalmology.

However, compared with the more tightly written and highly informative currently available textbooks it appears to be verbose and long-winded. The use of lists and diagrams to summarise a particular disease and its complications would have avoided some of this criticism. It also attempts to deal with too much, so that many important subjects are inadequately discussed. Both the clinical and surgical management of many disorders are mentioned. Inevitably in a book of this size the surgical treatment of many of the disorders is dealt with only superficially, and this aspect could safely have been excluded and left to the specialist surgical textbooks. For instance, in the treatment of congenital cataract by aspiration, only the push/pull method has been described, although there are many alternative methods available, including the use of modern aspiration machines.

Some curious omissions arise. The assessment of macular function in the presence of a dense cataract makes no mention of the Maddox rod test, the definition of optic nerve atrophy is poor, and the indications for corneal grafts are not complete, there being no place in modern surgery for the use of lamellar graft for herpes simplex keratitis, as the recurrence rate is so high. The clinical description of herpes zoster ocular involvement is poor, there being no mention of any epithelial disorders. The optic section is inadequate, and could safely have been left to more specialised optics books. There is no mention of the optics of any instruments, there are no diagrams of the optics of refraction (and do people still use a mirror and lamp, and not a streak retinoscope, nowadays?). Not everyone would agree with atropic refraction for children, when modern cycloplegics are available. A section on spectacle intolerances would have been appreciated, and the section on ocular pharmacology is much too brief, with no mention of the action of drugs on the pupil. In the section on prisms no mention is made of their therapeutic use in orthoptic exercises.

The book serves as an easily read introduction to ophthalmology.

JAMES McGILL

Atlas of Ophthalmic Ultrasonography and Biometry. By H. J. SHAMMAS. Pp. 321. £40·00. C. V. Mosby: St. Louis. 1984.

This book contains seven chapters, an appendix, and a glossary of terms. The first chapter, entitled 'Basic physics, technology and instrumentation,' is useful to the extent that it describes some of the jargon peculiar to ophthalmic ultrasound, as does the glossary of terms at the end of the book. Commercially available ophthalmic ultrasound instrumentation including biometric units are discussed, and the published B scans were taken using three mechanical sector systems (Ocuscan 400 from Sonometrics Systems Inc., the Ultrascan 11 from Xenotech-Cooper Medical Devices Corporation, and the Bronson-Turner unit from Storz Instrument Company). The A scans were obtained using the Kretz 7200MA ophthalmic A scan system.

The 'meat' of the book is an attempt to correlate ultrasonic findings in vitreoretinal disorders (including trauma and foreign bodies) and tumours (both intraocular and orbital) with their pathological basis and clinicosurgical implications. The page layout for this exercise is attractive, but the associated text tends to be oversimplified and confusing at best and is utterly misleading at worst. The B scan criteria of choroidal detachment, for example, are described as multiple areas of convex echogenic lines which do not involve the nerve head, so that the pathognomic signs of anterior extension to the scleral spur and tethering of the vortex ampullae and short ciliary artery insertions are left either to the reader's own extrapolation or to his imagination. The pathogenic sequences are remarkable for their naivity. We are variously informed that fibrous vitreous membranes are caused by organisation of vitreous haemorrhage; that vitreous membranes get thicker, attach to the retina, and cause traction retinal detachments on follow-up; that the coronal membrane of the triangle in massive preretinal retraction is a cyclitic membrane, etc. Remarkably, the text on vitreoretinal pathology (including that from trauma) never actually mentions the fundamentals, that is, the vitreous base and the concept, causes, and effects of epiretinal membranes.

The author stresses the value of A scan techniques in orbital diagnosis and follows the views of Ossoinig especially in measurement of the optic nerve diameter and ocular muscle thickness; the fact that such measurements defy the application of natural physical laws to the orbit should not be overlooked. Thus sections on the limitations of ultrasound in intraocular and orbital diagnosis would have benefited from expansion.

An excellent final chapter on axial length measurement and intraocular lens implant power calculation summarises the diversity of equipment, formulae, and opinions. An appendix of conversion tables of microseconds to millimetres in ocular tissue (lens, vitreous, and aqueous) follows the final chapter.

In summary, this book is well presented, and the examination techniques used are clearly explained. Any grey-scale deficiencies in published B scans reflect the inadequacies of the commercially available mechanical sector scanners. It is refreshing to note that most of the examinations from which photographs have been published have been performed by the author. The book is suitable for those starting out in ophthalmic ultrasound, and gives the author's opinions on the best way to examine various conditions. It will allow beginners a basis for forming their own opinions on their techniques of choice.

MARIE RESTORI
DAVID McLEOD

Johnny Gets Some Glasses. By NIGEL SNELL. Pp. 27. 85p. Hamish Hamilton: London, 1984.

Any attempt to relieve the public of some of its misconceptions about eyes and spectacles is to be welcomed, and the children's book under consideration is undoubtedly an attempt towards this end. It seemed appropriate that those particularly dealing with children, namely orthoptists, might be asked for their comments, and, as would be expected, these proved to be very pertinent. It was strongly felt that the reference to 'weak eyes' was inappropriate and the punitive image of teachers who make the poorly sighted sit in front of the class hardly helpful. Confusion arises between a visit to the opticians and being met by doctors, while it is also legitimate to wonder if the use of dyslectic style lettering in the final picture is appropriate in a text designed for reading learners.

It is regretted that, although the book is certainly written in an amusing and sympathetic style, which is the aim of the series, the present example can only be regarded as having scored at best an 'outer.' Sad, for a little more consultation might well have produced a very worthy bullseye.

M. J. GILKES

Traumatology of the Skull Base. Eds. M. SAMII AND J. BRIHAYE. Pp. 240. DM98. Springer-Verlag: Berlin. 1983.

This book is a collection of papers presented at the first international meeting of the Skull Base Study Group in Brussels in 1982. There are 39 contributors, and some of the papers will be of interest to ophthalmologists, in particular those on the subject of the optic nerve and the orbit, including the treatment of orbital fractures, optic nerve injuries, and ocular palsies. The authors with few exceptions work on the Continent of Europe and are writing in English, which at times makes for rather awkward style.

C. J. EARL

Notes

OSUK Annual Congress

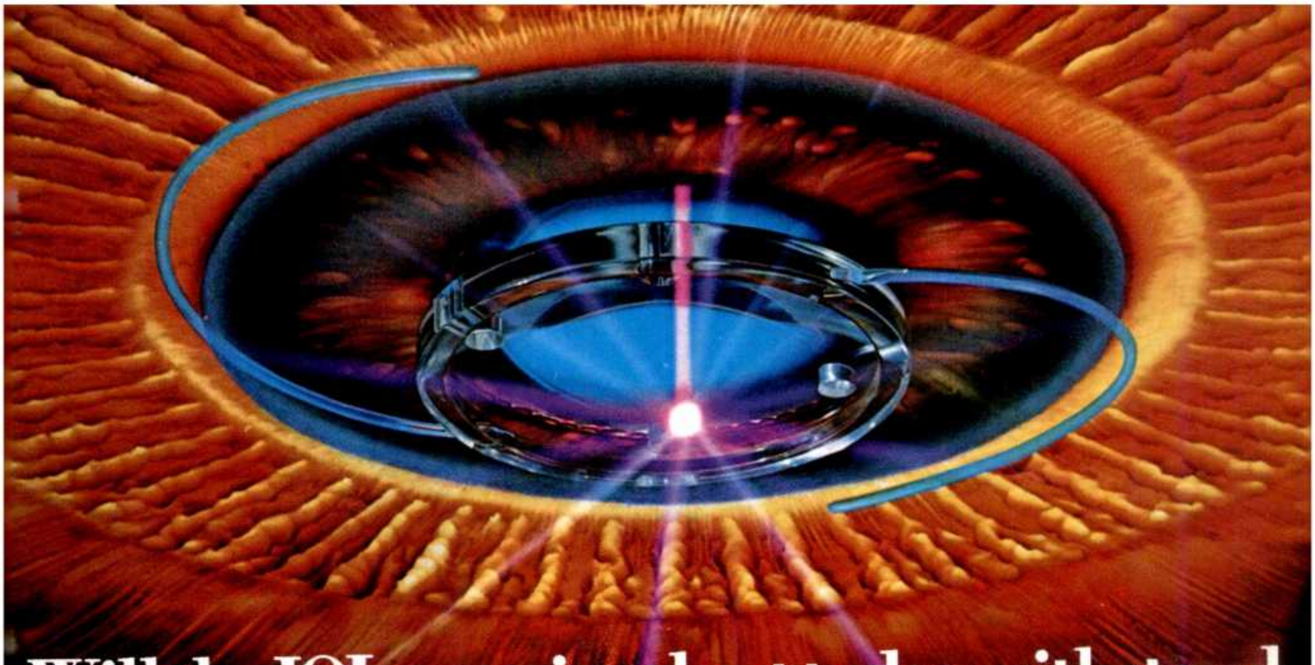
The 1985 Annual Congress of the Ophthalmological Society of the UK will be held on 17–19 April at the Harrogate Conference Centre, Harrogate, North Yorkshire. Group rates for accommodation have been negotiated at the Majestic Hotel, Ripon Road, Harrogate, N Yorkshire HG1 2HU (tel. Harrogate 68972). Further information on accommodation may be obtained from Tourist Information Centre, Royal Baths Assembly Rooms, Crescent Road, Harrogate HG1 2RR (tel. Harrogate 65912).

Canadian Ophthalmological Society

This society will hold its 48th Annual Meeting on 23-26 June 1985 at the Toronto Hilton Harbour Castle Hotel, Toronto, Ontario, Canada. Details from Canadian Ophthalmological Society, PO Box 8844, Ottawa, Ontario, Canada K1G 3J2.

Colour vision deficiencies

The 8th Congress of the International Research Group on Colour Vision Deficiencies will be held on 23–26 June 1985 in the Palais des Papes in Avignon, France. Themes will include aging of the eye, effect of intoxications, and visual effect of intense light. Details from Dr Vola Jean, 38 rue Jean Mermoz, 13008 Marseille, France.



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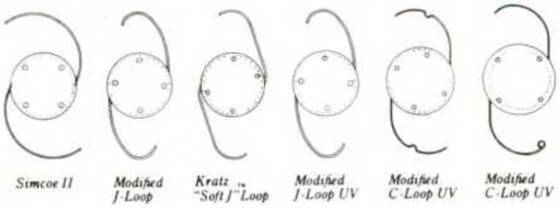

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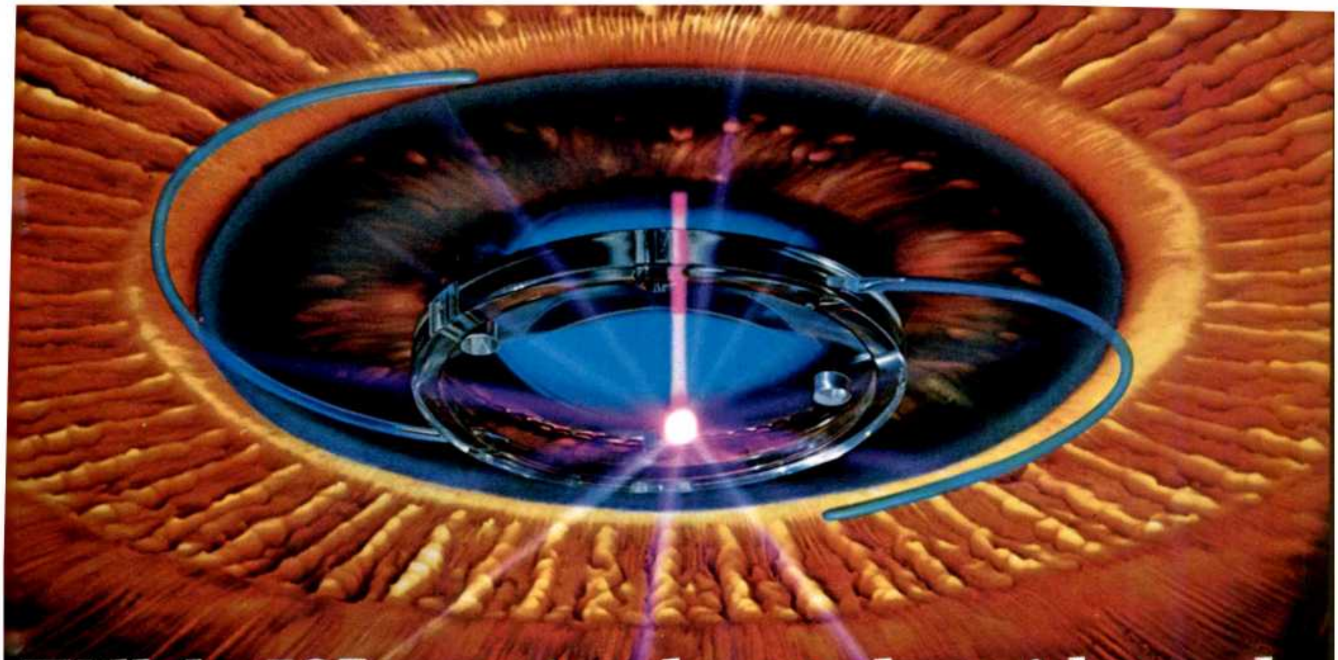

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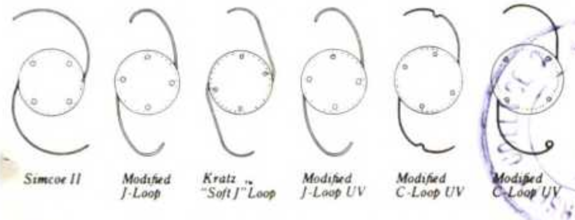

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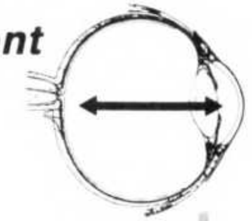

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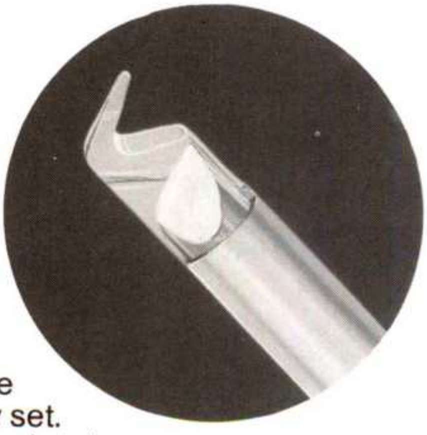

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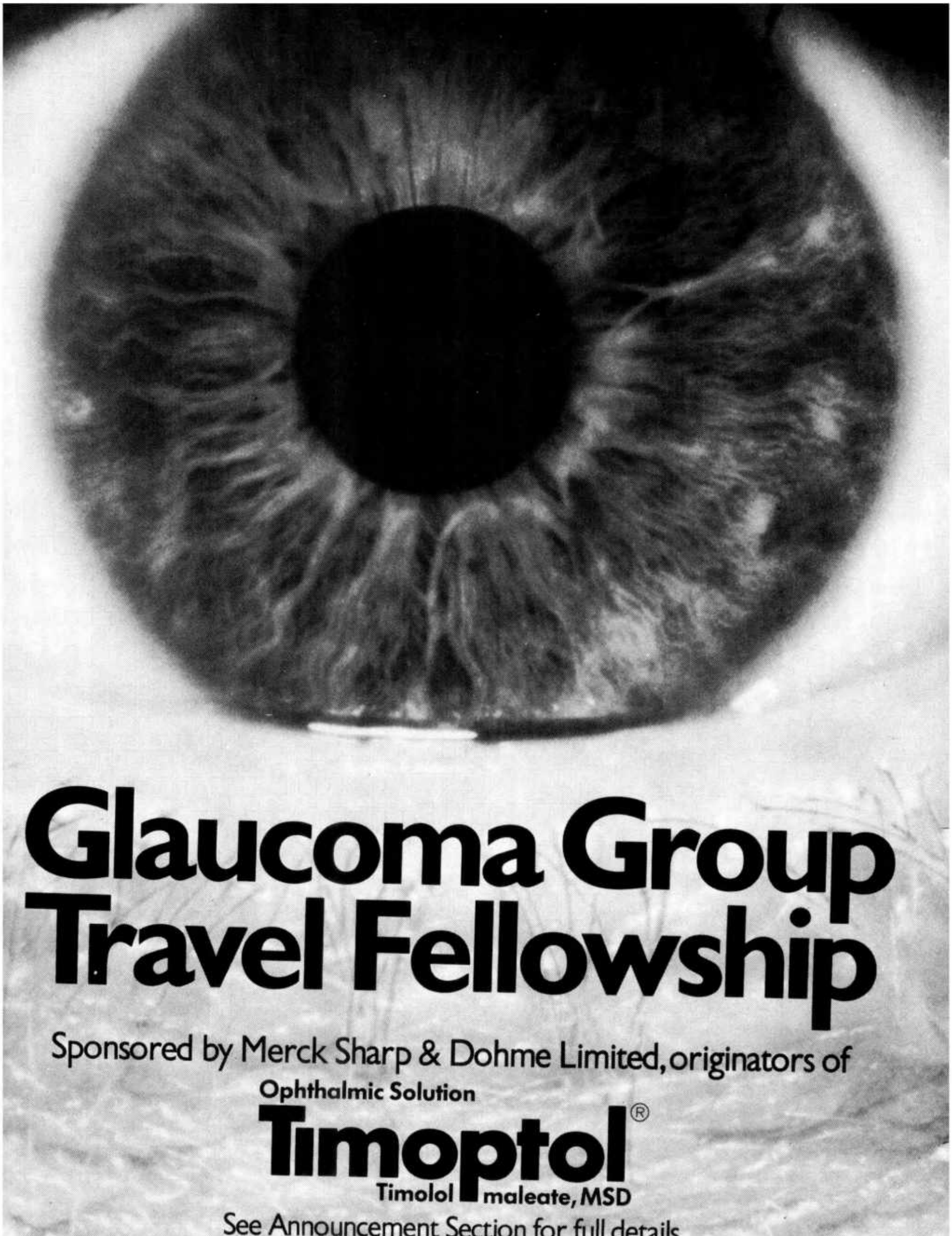

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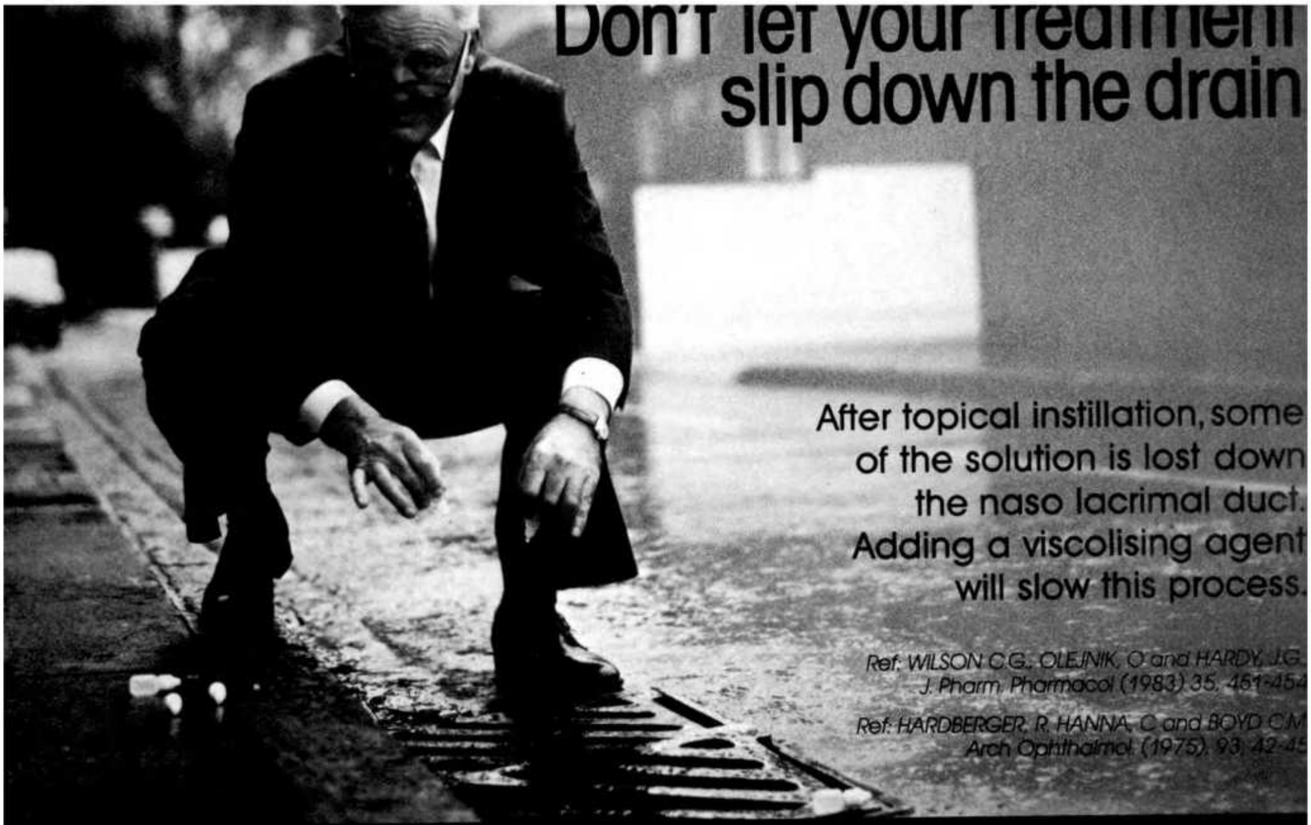

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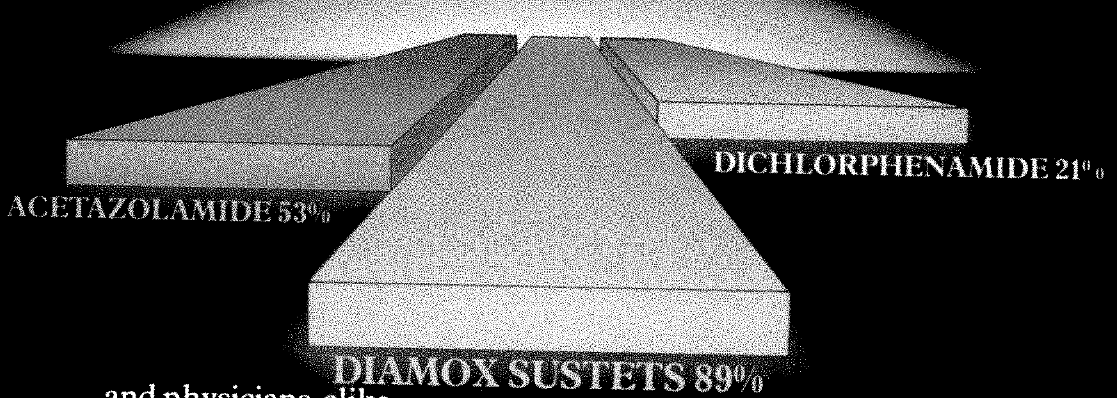

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Photocoagulation for peripheral neovascularisation in diabetes

D V INGLESBY, G S TURNER, W E SCHULENBURG, AND E M KOHNER

From the Department of Medicine, Hammersmith Hospital, Du Cane Road, London W12 0HS

SUMMARY A study of 90 eyes in 72 diabetic patients with peripheral retinal neovascularisation treated by photocoagulation indicated that the subsequent development of further peripheral or disc new vessels is infrequent if panretinal photocoagulation is the initial treatment procedure. Focal or sectorial treatment may be considered only if a small area of neovascularisation is present initially and provided regular follow-up can be guaranteed.

New vessel proliferation from the optic disc, the retinal surface, or the surface of the iris occurs as a complication of diabetes and is presumed to be a response to widespread retinal ischaemia. The treatment of disc new vessels (NVD) has now been rationalised as the result of many studies, the most impressive of which have been the Diabetic Retinopathy Study (DRS) in the United States,[1] and the British Multicentre Study.[2] The progress of iris neovascularisation can be arrested or even reversed if fibrotic changes are absent.[3] In both of these conditions the most effective treatment is panretinal photocoagulation (PRP), applied either by means of the xenon arc or the argon laser. The effect of each on NVD is similar, though the use of argon is accompanied by fewer side effects.[4 5]

The best form of management of peripheral retinal neovascularisation (new vessels elsewhere; NVE) is undecided. The presence of such vessels constitutes a threat to vision because of the potential for haemorrhage, though the risk is not of the same order as that posed by NVD. However, if NVE are accompanied by preretinal or vitreous haemorrhage, the eye enters the 'high risk' category of the DRS.[4] This fact has caused many ophthalmologists to treat eyes with NVE before high risk characteristics become manifest. The generally accepted treatment consists of focal or sectorial photocoagulation, with PRP being employed for those cases with widespread NVE.[6] The original policy of this unit, to employ focal treatment only, was influenced by the work of Okun *et al.*[7] However, the clinical impression gained in the unit over 15 years of treating such eyes is that those receiving focal or sectorial treatment progress to develop further new vessels with such regularity that PRP is now usually undertaken as the initial procedure, despite there having been no formal change in policy (Fig. 1).

Correspondence to Dr D V Inglesby, Moorfields Eye Hospital, City Road, London EC1V 2PD.

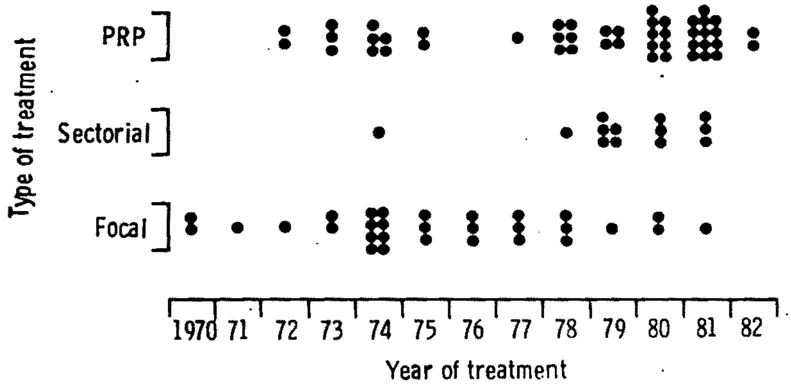

Fig. 1 *Distribution of types of treatment, 1970–82. (PRP=panretinal photocoagulation).*

The present study was performed to test this clinical impression—that is, to determine what proportion of eyes in each of the three treatment groups (focal, sectorial, PRP) proceeded to further neovascularisation after the initial treatment, and whether this progression was related to the extent of new vessel formation at that time.

Patients and methods

All the patients were attending the Diabetic Retinopathy Clinic at the Hammersmith Hospital and were treated between 1970 and 1982. The notes of all patients treated for NVE were inspected. Seventy-two patients were included in the study, of whom 25 were female, accounting for 30 of the 90 eyes studied. Fifty-eight of the patients were being treated with insulin, the remaining 14 being controlled on oral hypoglycaemic agents. The age at onset of diabetes ranged from 2 to 61 years (mean 27 years). The mean duration of known diabetes at the time of diagnosis of NVE was 15 years (Table 1). The mean age at diagnosis of NVE was 42 years (range 22–64 years). None of the eyes in the study had received photocoagulation for any reason prior to the NVE being treated, nor had any of the patients undergone pituitary ablation.

NVE were defined as those new vessels arising from areas of the fundus more than one disc diameter away from the optic disc. All patients had colour photography of the eyes, and usually but not invariably fluorescein angiography, performed prior to treatment. Included in the study were those displaying NVE in these pictures as well as those who were recorded in the notes (in the opinion of a consultant ophthalmologist) as having had NVE outside the field of the standard retinal photographs as defined in the Hammersmith Hospital Grading System.[8] In none of the eyes were NVD present at the time of the initial treatment, nor was there more than a trace of fibrous retinitis proliferans in any eye. Excluded from the study were those eyes displaying fluorescein leakage from the disc even if NVD were not recorded in the notes or observed on the colour photographs. Excluded also were those eyes thought to display grade 1 NVE but which did not show the characteristic leakage of fluorescein; such lesions would today be considered to be intraretinal microvascular abnormalities.

Table 1 *Age of onset and duration of diabetes at time of diagnosis of NVE in individual eyes*

Known duration of diabetes at diagnosis of NVE (years)	*Age at onset of diabetes (years)*			*Total*
	0–29	*30–59*	*≥60*	
0–5	0	12	1	13
6–10	1	3	0	4
11–15	15	7	0	22
16–20	15	10	0	25
21–30	16	6	0	22
>30	4	0	0	4
Total	51	38	1	90

TREATMENT

Focal photocoagulation treatment implies that given to the retina underlying the area of NVE, with a rim of adjacent retina being incorporated. Sectorial treatment involves in addition the creation of burns in a sector of the more peripheral retina, generally about an arc of 60°, with the site of NVE being within the apex of the sector. PRP implies clusters of burns around the foci of NVE with widespread scattered treatment in the remainder of the retinal periphery. Obviously the density of such treatment may vary. An arbitrary distinction was made here between 'light' and 'dense' PRP, the former being fewer than 2400 argon laser burns of 500 µm size, or fewer than 200 xenon burns 4·5° in size. Forty-seven eyes received PRP, 13 received sectorial treatment, and 30 had focal treatment. Fifty-six of the eyes were treated with the argon laser.

After treatment all patients were followed up for at least two years, the maximum being 13 years, mean five years. During this time examinations were regularly carried out, at least three times annually. Colour photographs were taken at least annually. Further neovascularisation was therefore detected and treated promptly when it occurred, PRP generally being applied on these occasions.

Statistical methods. The significance of the findings was assessed by the χ^2 method.

Results

Of the 90 treated eyes 31 (34%) developed subsequent neovascularisation (NVD in seven cases, NVE in 24 cases). The mean duration from treatment to NVD formation was two years, (range one month to seven years), and that from treatment to further NVE appearance was 2·5 years (range nine months to eight years). Seven of 47 eyes receiving PRP developed further new vessels, compared with 6/13 receiving sectorial, and 18/30 receiving focal treatment. Of the seven which had received PRP four had 'light' PRP (mean 1800 argon burns). A further eye receiving only 1000 argon burns later developed rubeosis iridis and then received further treatment. These results showed a significant ($p<0{\cdot}001$) difference in favour of PRP over focal treatment, and a less significant ($0{\cdot}01<p<0{\cdot}02$) advantage over sectorial treatment in preventing further neovascularisation (Fig. 2).

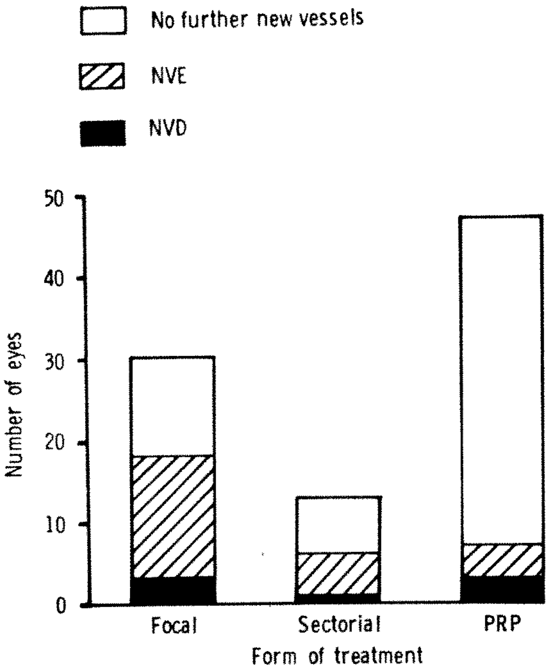

Fig. 2 *Subsequent development of new vessels in eyes grouped according to type of initial treatment. (PRP=panretinal photocoagulation).*

The histograms in Fig. 3 illustrate the eyes in four groups corresponding to the number of retinal quadrants containing NVE at the time of the initial treatment, and show the proportion of eyes which developed NVD or NVE for each mode of treatment in each group. It can be appreciated that in each of the four groups PRP was associated with a smaller incidence of further new vessel formation than were the other forms of treatment, but that the numbers involved were too small to apply the χ^2 test.

The proportion of eyes in each group that received argon or xenon treatment is demonstrated in Fig. 4, showing those eyes that developed further new vessels in addition to the group as a whole. It can be seen that there was no difference in this series between argon and xenon treatment in terms of the likelihood of subsequent new vessel formation.

The best corrected visual acuity before treatment was generally better than 6/12. Only 14 eyes were between 6/12 and 6/60. After treatment, and apart from temporary changes, there was loss of two lines (Snellen) in three eyes and loss of one line in eight eyes. Two eyes improved by two lines, six by one line; 71/90 remained the same. No record was made of visual field changes.

Discussion

Oosterhuis *et al.*[9] state that 'in patients with peripheral new vessel formation photocoagulation

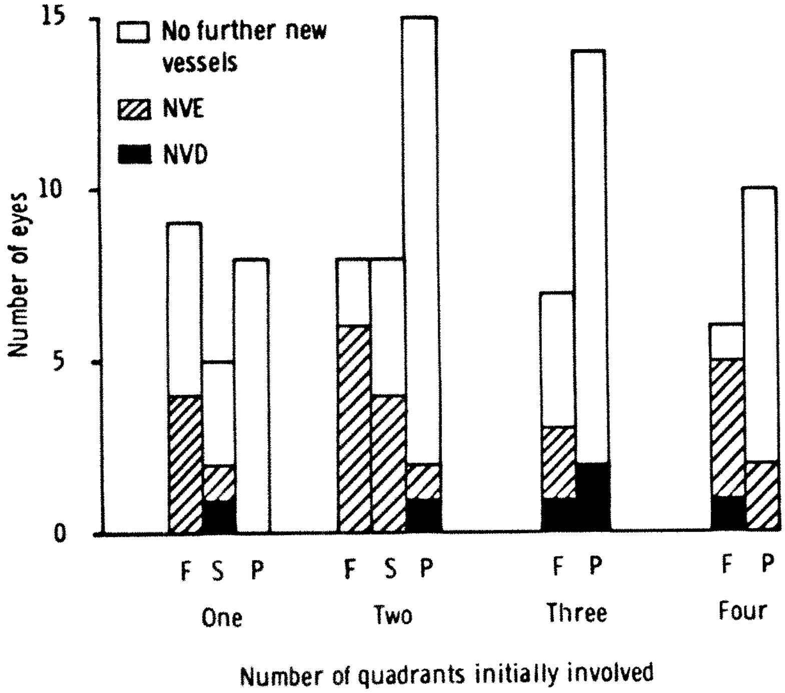

Fig. 3 *Subsequent development of new vessels in eyes grouped according to number of retinal quadrants initially containing NVE, and type of treatment received. (F=focal; S=sectorial; P=panretinal photocoagulation).*

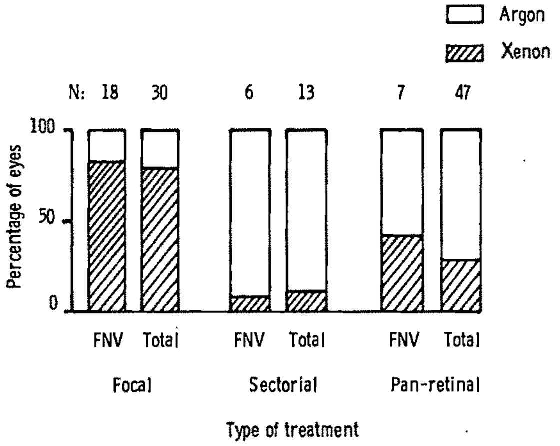

Fig. 4 *The proportion of eyes treated with the argon laser or the xenon arc; the left-hand column of each pair indicates those which subsequently developed further new vessels (FNV), the right-hand column shows all eyes in that treatment group.*

must be performed before disasterous complicating lesions such as vitreous haemorrhage, glial strands, or signs of shrinkage have developed.' The DRS, in referring to eyes with proliferative retinopathy but without high risk characteristics, asks if the extensive scatter treatment used in the study was necessary, whether less extensive treatment might suffice, or whether in fact it might be safe or even wise to defer treatment.[1] We feel, like Oosterhuis *et al.*, that treatment is necessary because the presence of such lesions is a definite risk to vision, although in a small proportion of cases the abnormal vessels may regress spontaneously,[10] as do 4% of NVD.[4] Eyes with moderate or severe NVE, if associated with vitreous or preretinal haemorrhage (i.e., in the high risk group) develop vision of less than 5/200 in 36·8% cases over a two-year period,[11] and eyes with any grade of NVE have a definite and increased risk of developing high risk characteristics if left untreated.[4] This finding has recently been confirmed in the report of the British Multicentre Study,[2] which showed that 50% of untreated eyes containing NVE developed NVD within five years. Also to be remembered is the fact that, even with treatment, eyes with high risk features still have an appreciable chance of going blind (12–15%) in five years.[1 2] However, as the authors of these figures are careful to point out, they include some eyes that were diagnosed and treated at a more advanced stage than would be the case with regular surveillance of cases progressing from the milder stages of disease.

Against this background many ophthalmologists advocate the tretment of NVE, but there are no reports concerning this matter specifically, and there is no consensus as to the most appropriate method. The presence of NVE indicates retinal ischaemia, and from fluorescein angiography it is usually apparent that ischaemia is widespread even if only one or two small foci of NVE are present. Therefore focal treatment, although removing the immediate source of risk to the eye, will not remove the continuing stimulus to further neovascularisation. Not surprisingly, therefore, the present study shows that, overall, PRP is more effective than less extensive treatment in preventing subsequent neovascularisation. This is in agreement with the British Multicentre Study, which found that 12 eyes treated for NVE and which later developed NVD had had less treatment than the 30 which did not progress in this way.[2]

One criticism of the data presented here is that the group receiving focal treatment has been followed up for a longer period than those receiving PRP or sectorial treatment (Fig. 1). However, we have shown that the mean duration between treatment and the development of further new vessels is from two to 2·5 years, and all eyes have been followed for at least two years. In addition Oosterhuis *et al.* found that in the latter three years of their five-year post-treatment follow-up most of the eyes were in a relatively stable situation, so we believe that no great error has been incurred by our comparison of the treatment groups.

It is to be remembered that even in capable hands the application of PRP with the argon laser imparts a small risk to central vision, and peripheral field and night vision are slightly impaired. However, we consider that PRP is the appropriate form of treatment as the initial procedure for most eyes displaying NVE. Limited treatment should be reserved only for those few eyes with very early NVE, without widespread ischaemia, in patients who can be thoroughly examined regularly.

The authors acknowledge the work of the ophthalmologists and photographers who worked in the unit during the period of management of the patients in the study.

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References

1 Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: clinical applications of DRS findings. Report number 8. *Ophthalmology* 1981; **88:** 583–600.

2 British Multicentre Study Group. Photocoagulation for proliferative diabetic retinopathy: a randomised controlled clinical trial using the xenon-arc. *Diabetologia* 1984; **26:** 109–15.

3 Little HL, Rosenthal AR, Dellaporta A, Jacobson DR. The effect of pan-retinal photocoagulation on rubeosis iridis. *Am J Ophthalmol* 1976; **81:** 804–9.

4 Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of DRS findings. *Ophthalmology* 1978; **85:** 82–106.

5 Plumb AP, Swan AV, Chignell AM, Shilling JS. A comparative trial of xenon-arc and argon laser in the treatment of proliferative diabetic retinopathy. *Br J Ophthalmol* 1982; **66:** 213–8.

6 Morse PH. Rationale for the treatment of diabetic retinopathy. *Trans Ophthalmol Soc UK* 1976; **96:** 86–9.

7 Okun E, Johnston GP, Boniuk I. *Management of diabetic retinopathy: a stereoscopic presentation.* St Louis: Mosby, 1971: chapter 5.

8 Oakley NW, Hill DW, Joplin GF, Kohner EM, Fraser TR. Diabetic retinopathy. 1. The assessment of severity and progress by comparison with a set of standard fundus photographs. *Diabetologia* 1967; **3:** 402–5.

9 Oosterhuis JA, Beintema MR, Lemkes HHLM, Nikkels R, Terpstra J. Photocoagulation treatment in diabetic retinopathy: a two-year pre- and five-year post-treatment study. *Doc Ophthalmol* 1979; **48:** 101–62.

10 Dobree JH. Proliferative diabetic retinopathy: evolution of the retinal lesions. *Br J Ophthalmol* 1964; **48:** 637–49.

11 Diabetic Retinopathy Study Research Group. Preliminary report on effects of photocoagulation therapy. *Am J Ophthalmol* 1976; **81:** 383–96.

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Physiological and pathobiological significance of ocular glycoproteins. I. Studies using fluorescein labelled glycine max

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SUMMARY Cell surface carbohydrates play an important role in several biological, immunological, and neoplastic phenomena including development, growth regulation, cellular locomotion, receptor activation, and tumour metastasis. Fluorescein labelled lectins which bind to specific carbohydrate residues in glycoproteins and glycolipids are being increasingly used as chemical probes to study cell components. Several different preparations of ocular tissues from human, rabbit, and rat were examined for the distribution of N-acetyl-D-galactosamine (D-gal NAc) by means of fluorescein-labelled lectin from soybean (glycine max). A very strong fluorescence was observed in the corneal epithelium; Descemet's membrane and corneal endothelium were also strongly fluorescent. The conjunctival epithelium similarly showed a strong reaction, as did the goblet cells. The iris epithelium and the dilator pupillae were only weakly fluorescent, but the ciliary body showed strong fluorescence, as did the blood vessels. As compared with lens fibres the lens epithelium was strongly fluorescent. The outer retina, that is, the photoreceptors, the pigment epithelium, and Bruch's membrane, showed a very strong reactivity. The optic nerve showed moderate fluorescence, but reaction with extraocular muscles was variable. The skin of the upper and lower eyelids, hair follicles, and blood vessels showed strong lectin binding. Sections of retinoblastoma and malignant melanoma showed no reaction. The physiological and pathological significance of these findings is discussed.

About 5% of mammalian cell membrane consists of carbohydrates which are usually associated with glycoproteins, and it is widely recognised that these determine the 'individuality' of a cell and regulate its behaviour, growth, division, and differentiation. Glycoproteins also constitute the antigenic determinants in a given tissue, act as receptors for hormones, mitogens, drugs, and micro-organisms, and provide markers of cellular identity.[1] Furthermore, cells recognise and interact with each other through surface glycoproteins, sugars acting as a method for cellular communication. The activity of the corneal endothelium, the ciliary epithelium, the photoreceptors, and the retinal pigment epithelium depends on the influx of certain ions and nutrients and eflux of other ions and metabolites, which in turn are dependent on cell surface glycoproteins.

Our understanding of cellular glycoproteins has greatly increased since the discovery of lectins, which

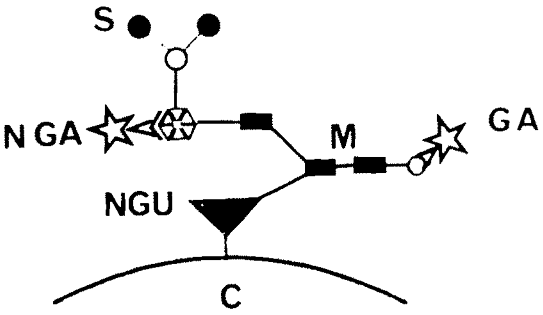

Fig. 1 *A typical oligosaccharide sequence in the glycoproteins of cellular surface (c) is illustrated. The stars represent fluorescein labelled lectin. Glycine max binds predominantly to NGA and to a less extent to galactose moiety. M=Mannose. NGA=N-acetyl galactosamine. GA=Galactose. NGU=N-acetyl glucosamine. S=Sialic acid.*

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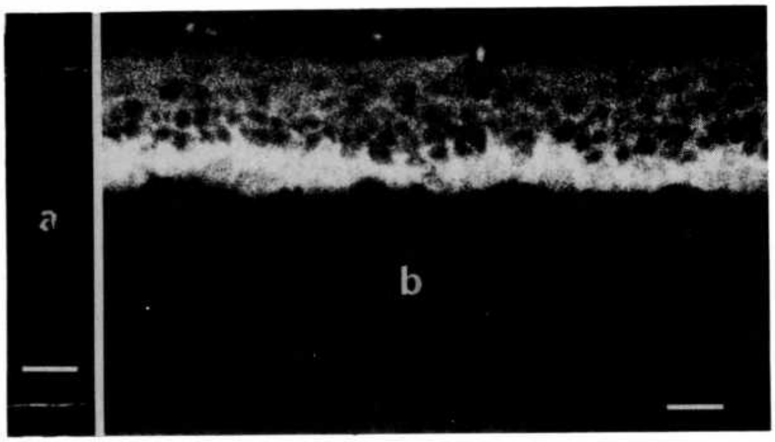


Fig. 2 *Normal rabbit cornea stained with fluorescein-labelled soyabean lectin.* (a) *The epithelium at the top and the endothelium at the bottom of the microphotograph are fluorescent. Bar=25 μm.* (b) *Higher magnification of the epithelial layer showing band-like fluorescence of the basal epithelium. Bar=10 μm.*

bind in vitro to carbohydrate moieties. Lectins are themselves proteins or glycoproteins and are derived from a wide variety of plants and animals. When labelled with fluorescein or other markers, these can be used to detect specific sugars in a given tissue. Since soybean lectin (glycine max) binds primarily to N-acetyl-D-galactosamine (D-gal NAc) residues in glycoproteins and glycolipids (Fig. 1), it has been advantageously used in the present study to examine the distribution and pathophysiological implication of this sugar in ocular tissues.

Materials and methods

Various normal and pathological tissues from human, rabbit, and rat eyes were processed for microscopical examination; small strips 5×5×5 mm were used. Tissues were fixed by immersion in a fixative; variation of the fixation methods included different immersion times (30 min to overnight) and several types of fixative—for example, 2·5% glutaraldehyde, 10% paraformaldehyde, 10% formalin (buffered at pH 7·3), and absolute methanol (analytical grade). After being washed in three changes of phosphate buffered saline (PBS), pH 7·3, for 30 minutes the specimens were dehydrated in graded methanol, cleared in cedar wood oil (British Drug Houses) with at least three changes, and embedded in paraffin wax. Sections 8 μm thick were prepared on a sledge microtome.

The introduction of cedar wood oil as clearing agent and paraffin as embedding material[2] has greatly simplified fluorescence microscopy of ocular tissues. Fluorescein isothiocyanate (FITC) labelled conjugates (Sigma Chemical Co.) were used in this study (2% in (PBS) for 10 minutes). According to the manufacturers the FITC-lectin conjugates were free of unbound fluorescein and were tested for their agglutinating reactivity on rabbit and human red

Table 1 *Demonstration of saccharide binding sites in ocular tissues by means of fluoresceinated lectin*

FITC lectin	*Glycine max*
Sugar	*D-gal NAc*
Conjunctiva:	
epithelium	+ +
goblet cells	+ + +
Cornea:	
epithelium	+ + +
Bowman's zone	+
stroma	+
Descemet's membrane	+ +
endothelium	+ + +
Sclera	+
Uvea:	
iris epithelium	−
ciliary body epithelium	++
choroid	+
trabecular meshwork	+
Lens:	
epithelium	+ + +
capsule	+
fibres	+ +
Retina:	
pigment epithelium	+ + +
photoreceptors	+ + +
ganglion cells	+
others	−
Optic nerve	+

Table 2 *Demonstration of saccharide binding sites in adnexal tissues of the eye by means of FITC lectin*

FITC lectin	*Glycine max*
Sugar	*D-gal NAc*
Eyelid:	
epidermis	+ + +
hair follicle	+ +
sweat gland	+ +
sebaceous gland	+
meibomian gland	+
Lacrimal gland	+
Harderian gland	+
Extraocular muscles	+ to + +
Ciliary nerves	+ + +

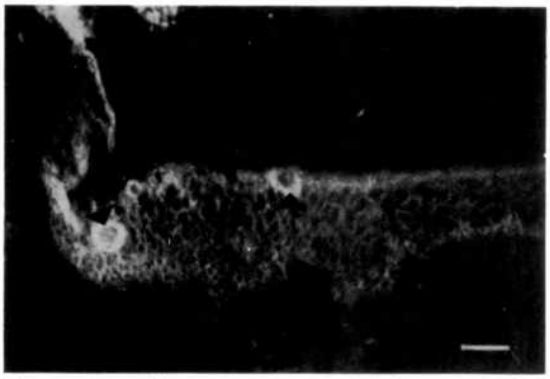


Fig. 3 *Normal human conjunctiva. Note the reaction of fluoresceinated lectin with the stratified epithelium and goblet cells (arrows). Bar=12 µm.*

blood cells. The lectin to fluorescein ratio was 1:0·67 and the lectin concentration was 31 µg/ml.

In our control experiments (i.e., neutralisation reaction) FITC conjugate was preincubated (2 h, 4°C) in 0·2 M solution of inhibitory sugar, D-gal NAc. The tissue sections were brought down to distilled water in the conventional way and then incubated for one hour at 37°C in the same solution. Fluorescence in these sections was completely eliminated when compared with sections exposed to the conjugate without the inhibitory sugar. Additional experiments were performed to determine whether or not the specificity of the lectin for sites in ocular tissues was altered because of conjugation with FITC. Tissue sections were treated with FITC-lectin conjugate to which various concentrations of the corresponding unlabelled lectin had been added. In each instance the addition of unlabelled lectin at appropriate concentrations caused a uniform decrease in the overall intensity of fluorescence but did not alter the pattern of fluorescence. These observations suggest that labelled and unlabelled lectin compete for the same sites in ocular tissues and thus support the view that conjugation of lectin to FITC does not alter its specificity. Sections were also exposed to 0·1 M FITC in 0·1 M phosphate buffered saline to exclude any non-specific binding, and 1% aqueous osmium tetroxide was used for one to two minutes to quench autofluorescence. Stained sections were examined under an epifluorescence microscope equipped with FITC interference filter.

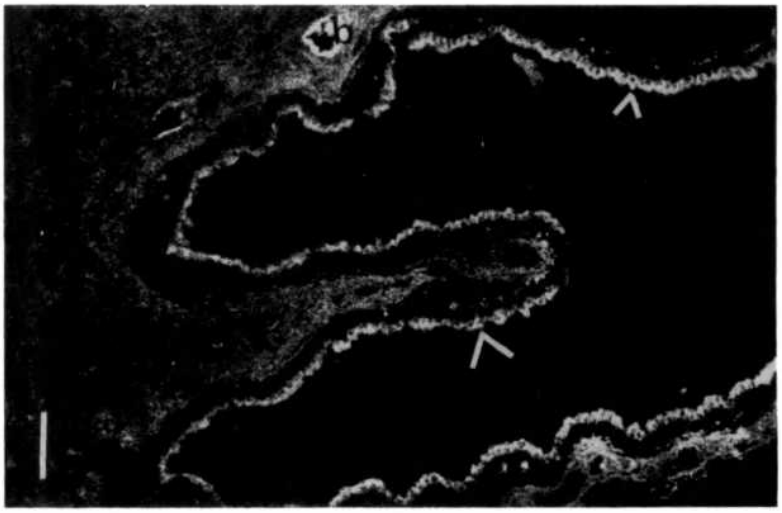
Results

Absolute methanol was found to be the most suitable fixative. The results obtained are summarised in Tables 1 and 2. The designations used in these tables to indicate fluorescence intensities (i.e., +, ++, etc.) were arrived at by comparing the reaction intensity of the conjugate with the control specimens containing the appropriate inhibitory sugar.

Cornea and conjunctiva. Sections of human and rat cornea treated with FITC-labelled soybean lectin showed strong (pericellular and cytoplasmic) fluorescence of the epithelium, particularly its superficial layers; in rabbits, however, the strongest reaction was present in the basal epithelial layer (Fig. 2). Corneal stroma was only weakly fluorescent, but Descemet's membrane and the endothelium were strongly reactive. The conjunctival epithelium and the goblet cells showed strong pericellular and diffuse cytoplasmic fluorescence respectively (Fig. 3); only weak fluorescence was seen in the sclera.

The uvea. The pigment epithelium of the iris along

Fig. 4 *Normal rabbit ciliary body. The reaction is chiefly in the non-pigmented epithelium* (arrows) and in the blood vessels (b) *Bar=18 µm.*



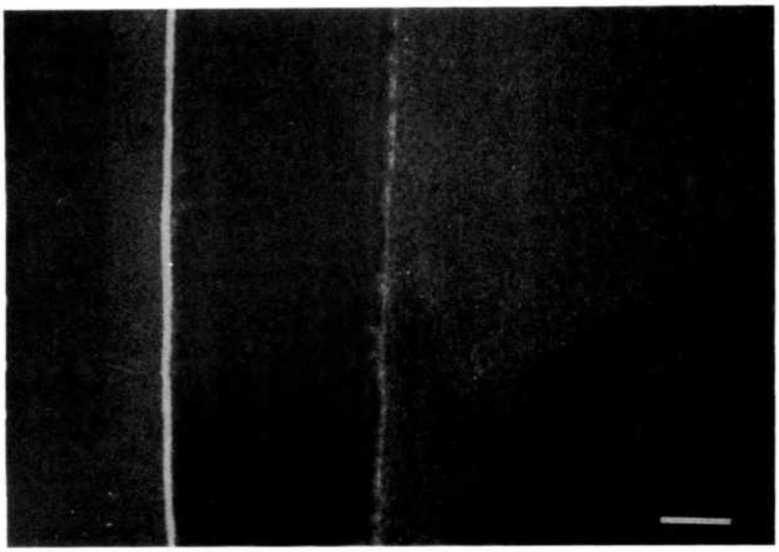


Fig. 5 *Normal rabbit lens stained with fluorescein-labelled soyabean lectin. A weak reaction with the lens capsule but a very strong reaction with the lens epithelium is recorded. Bar=18 μm.*

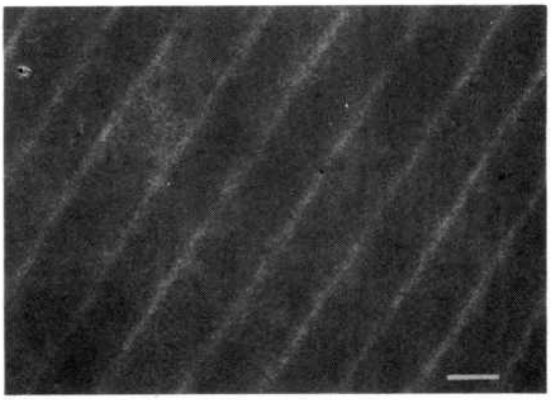


Fig. 6

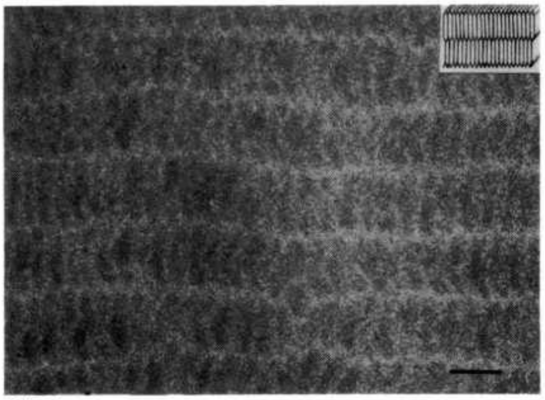


Fig. 7

Figs. 6 and 7 *The lens cortex cut at various angles to show lens fibres; a moderate fluorescence is present between lens fibres in the region of interlocking junctions. Bar=6 μm.*

with the dilator pupillae showed negligible fluorescence, but the ciliary epithelium was strongly fluorescent. Although the stroma showed weak fluorescence, the blood vessels were strongly fluorescent (Fig. 4). The choroid, apart from blood vessels, was unremarkable.

Trabecular meshwork. In contrast to the corneal endothelium, the meshwork cells showed only negligible fluorescence.

The lens. The zonule and the zonular lamellae were non-fluorescent. The capsule was only weakly fluorescent, but the lens epithelium showed a very strong fluorescence (Fig. 5). The rectangular or hexagonal cells of the lens cortex as seen in cross-section had a fairly homogeneous but weak cytoplasmic fluorescence. A rather strong reaction was present, however, along the sides of the hexagon where the interlocking processes of lens fibres are found (Figs. 6, 7).

The retina. The internal limiting membrane and the nerve fibre layer showed no reactivity, but there was a weak reaction in the ganglion cell layer. The internal plexiform layer, internal nuclear layer, and the external plexiform layer similarly showed no fluorescence. The outer retina consisting of the photoreceptors, the pigment epithelium, and the associated Bruch's membrane showed, however, a very strong reaction (Figs. 8a, b, c); the orbital portion of the optic nerve showed only moderate fluorescence.

Ocular adnexa. Extraocular muscles showed moderate to very strong staining reaction (Fig. 9). The epidermis, the hair follicles, and the blood vessels in the upper and lower eyelids showed strong fluorescence (Figs. 10, 11); Meibomian gland,

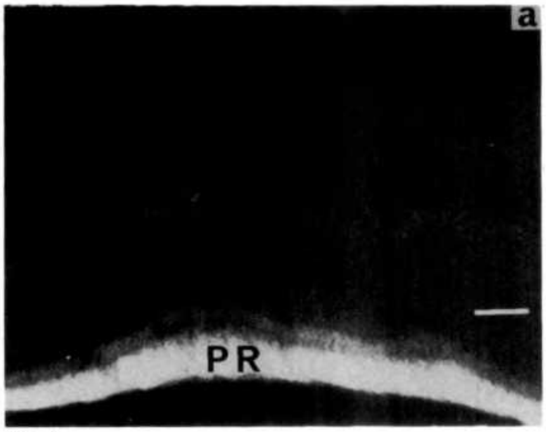


Fig. 8a

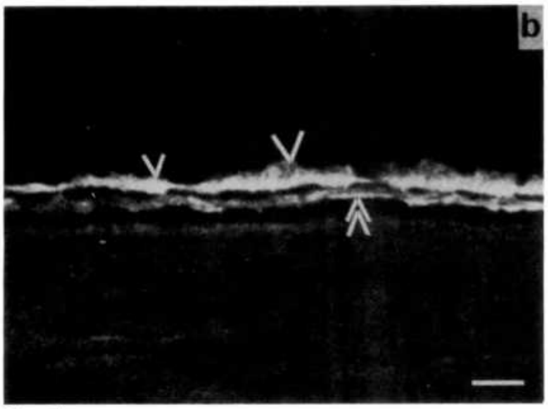


Fig. 8b

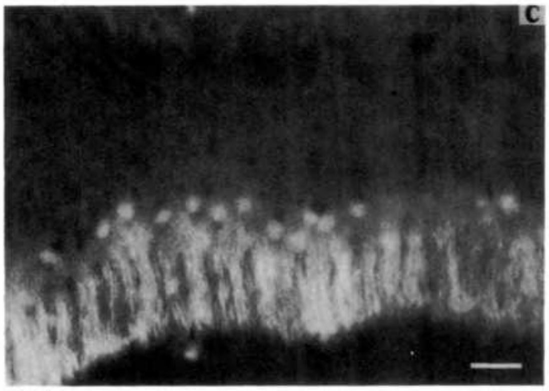


Fig. 8c

Fig. 8a, b, c *Normal rabbit retina. The external retina, i.e., the photoreceptors* (PR), *the pigment epithelium* (arrows), *and fluorescence. Bars* (a, b) = *18* µm, (c) = *10* µm.

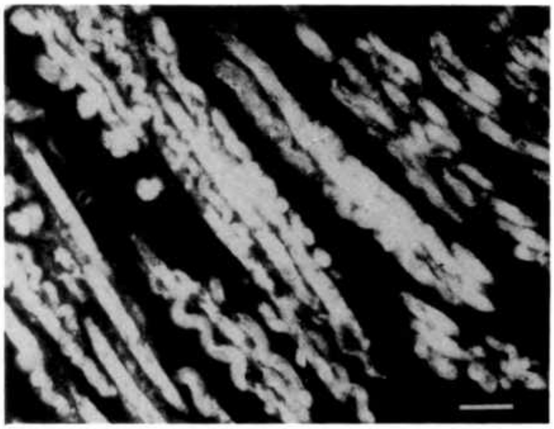


Fig. 9 *Extrinsic muscle of rabbit eye showing varying degrees of fluorescence when reacted with soybean lectin. Bar* = *18* µm.

sebaceous gland, and sweat gland (Fig. 12) were all moderately fluorescent. The ciliary nerve was strongly fluorescent, the optic nerve was moderately fluorescent, but the sciatic nerve which was used as a control showed a stronger fluorescence similar to that present in the ciliary nerve (Figs. 13a, b, c). Harderian and lacrimal glands were moderately fluorescent.

Ocular tumours. Since retinoblastomas arise in the sensory retina, sections of eyes with this tumour were treated with the same lectin. Whereas the photoreceptors gave the usual strong reaction, tumour cells apart from the feeding blood vessels were surprisingly non-fluorescent (Fig. 14). Areas of necrosis and haemorrhage showed, however, non-specific fluorescence.

Sections of malignant melanoma of the choroid were similarly non-fluorescent, but the overlying retinal pigment epithelium was strongly positive.

Discussion

The reactivity of soybean lectin with normal and neoplastic ocular tissues has not been so far fully investigated. The strong reaction in the superficial epithelial layers of human and rat corneae is comparable to that reported in the mucosal surface of the gastrointestinal tract.[3] The intercellular fluorescence (Fig. 2) and the fluorescence of the basement membrane is in keeping with light microscopic studies in which PAS-positive material is demonstrable at these sites.[4 5] Since the corneal stroma was only weakly fluorescent, it seems that the collagen and the intervening glycosaminoglycan have negligible amounts of D-gal NAc in addition to other carbohydrate residues reported before.[6] Alternatively D-gal NAc if present may be located very close

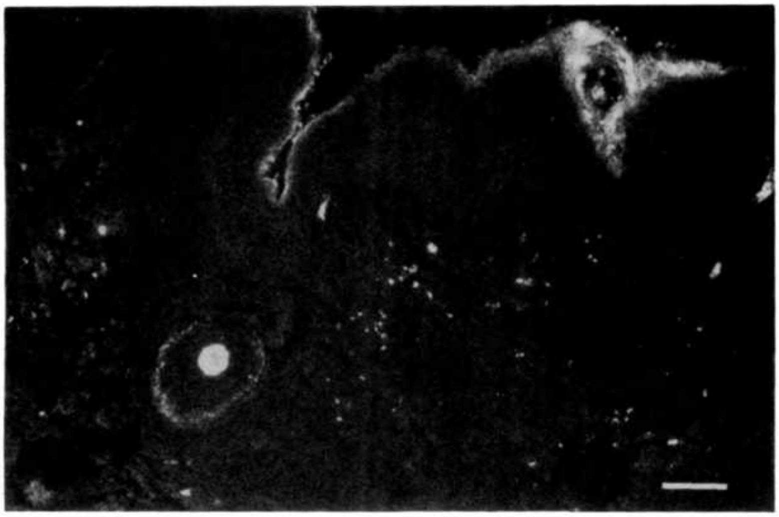


Fig. 10 *The skin of human upper eyelid showing fluorescence of superficial epidermis, hair follicle, and small blood vessels.*

to the molecule, as is the case with some other proteins[7 8] rather than at the ends of the carbohydrate side chains, and thus be inaccessible to the FITC-lectin conjugates. The strong fluorescence of Descemet's membrane and corneal endothelium is in keeping with light microscopic studies in which the presence of glycoprotein is well documented.[5 9] The conjunctival epithelium along with the goblet cells showed a strong reaction (Fig. 3), suggesting that these structures are rich in N-acetyl-glactosamine residues.

Since the epithelial cells lining the ciliary body and the iris are embryologically related, the absence of staining in the latter is most surprising. It may perhaps be related to functional differentiation of these two tissues, the ciliary epithelium being metabolically more active because of its involvement in aqueous humour production and elaboration of suspensory fibres of the lens.

Since the trabecular meshwork cells were negligibly fluorescent as compared with the corneal endothelial cells, it would seem that glycine max may be used as a marker for endothelial cells not only in tissue culture but also in histological preparations in conditions such as iris naevus syndrome, Chandler's endothelial dystrophy, and essential iris atrophy, in which the corneal endothelial cells supposedly grow over the trabecular meshwork and the adjoining surface of the iris. The strong fluorescence of photoreceptors may be due either to various glycoproteins within the visual cells[10-13] or to the acid mucopolysaccharide mantle around the photoreceptors[14] or perhaps both. Since the characteristic discs in the outer segment of photoreceptors are formed by infolding of the cell

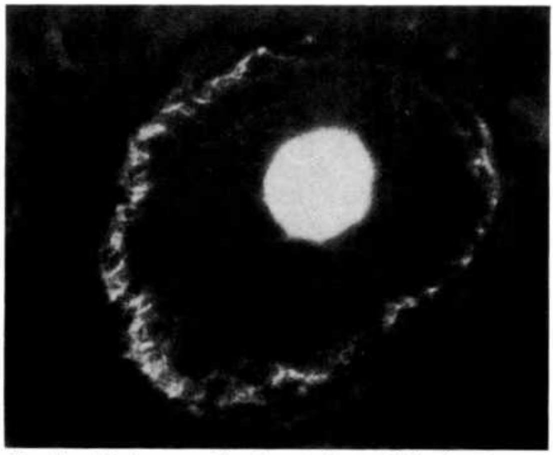


Fig. 11 *Higher magnification of a hair follicle showing central fluorescence of hair shaft and peripheral fluorescence of epithelial cells. Bar=6 µm.*

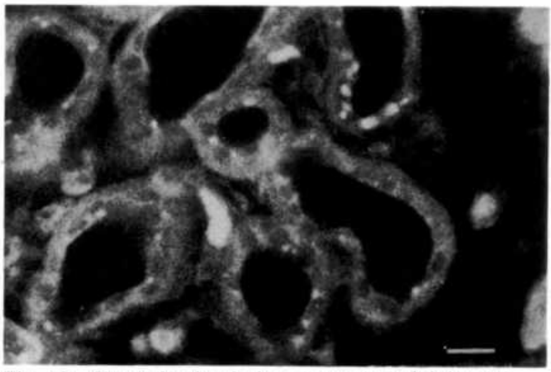


Fig. 12 *Sweat gland in the human upper eyelid showing moderate fluorescence. Bar=12 µ.*

Fig. 13 (a) *Optic nerve was moderately fluorescent.* (b) *Ciliary nerve and* (c) *sciatic nerve (used as control) were strongly fluorescent. Bars* (a)=*25* μm, (b)=*12* μm, (c)=*18* μm.

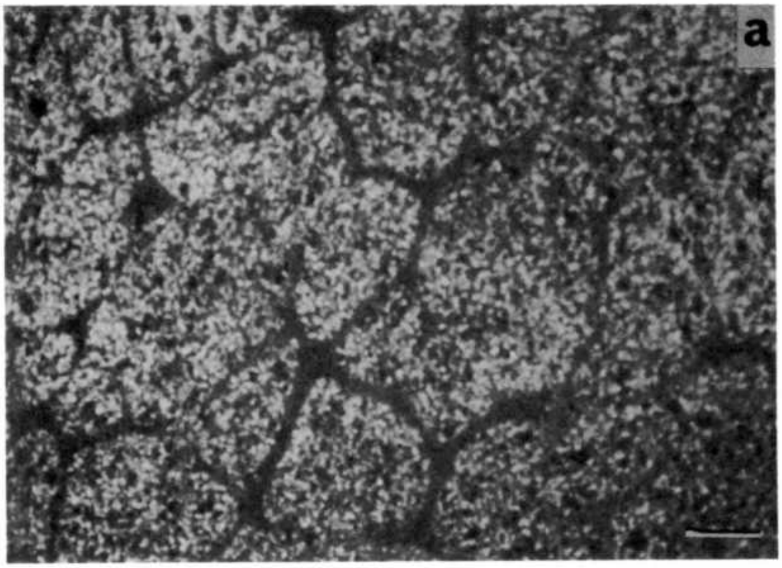


Fig. 13a

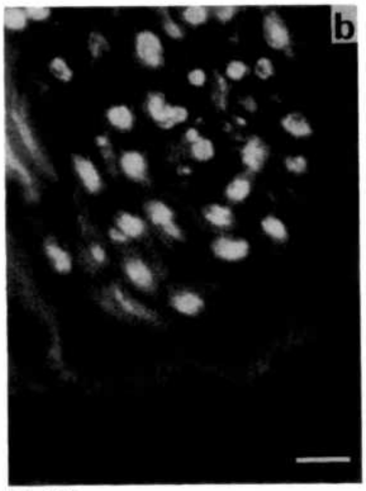


Fig. 13b

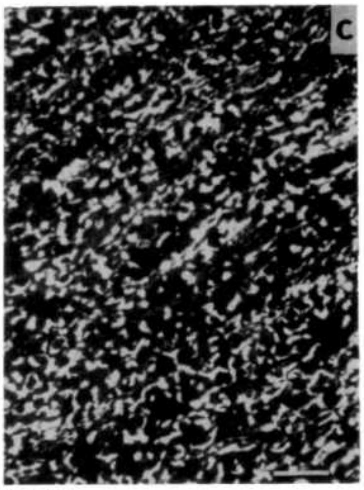


Fig. 13c

membrane, it is conceivable that some of the fluorescence was due to displaced membrane associated saccharides. In a recent study[15] it has been demonstrated that photoreceptors from dystrophic rats lack binding sites for various other lectins which avidly bind to normal visual cells. Whether this is true for glycine max is not known; we are currently investigating the role of the relevant saccharide in rod outer segment phagocytosis.

As compared with the ciliary nerves the optic nerve showed weaker fluorescence. This is of interest because it is known that these two nerves are differently myelinated. This phenomenon has not been reported before and needs further examination in view of the fact that peripheral nerve myelin is less effective in inducing autoimmune inflammation of the nervous system. It is concluded that D-gal NAc is widely distributed in ocular tissues, albeit in varying amounts, being most abundant in metabolically active sites such as the corneal epithelium and the endothelium, the ciliary and the lens epithelium, the photoreceptors, and the retinal pigment epithelium (Fig. 15).

Since retinoblastoma develops in the sensory retina and differentiates towards photoreceptors, we were surprised to find that the tumour cells did not

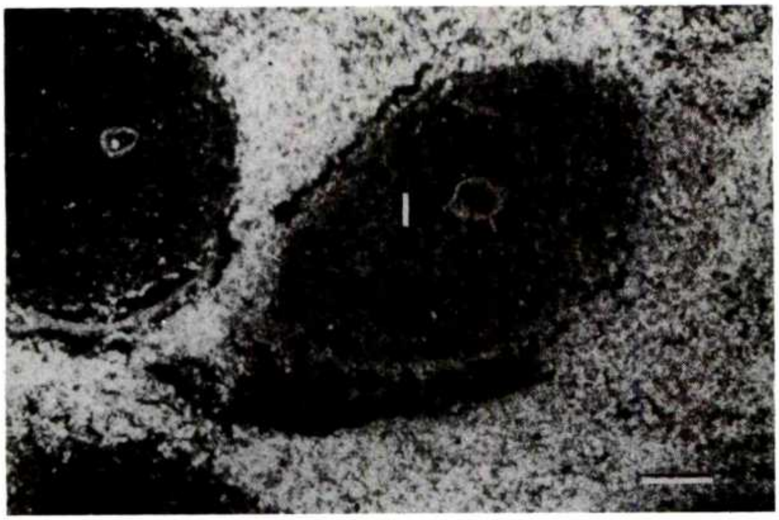


Fig. 14 *Section of retinoblastoma showing no fluorescence of viable cells around blood vessels* (B). *Necrotic cells in the periphery showed non-specific binding. Bar=12 µm.*

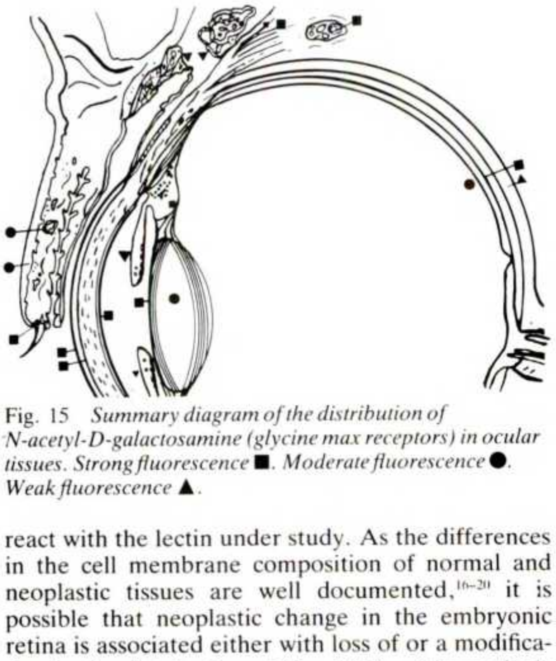


Fig. 15 *Summary diagram of the distribution of N-acetyl-D-galactosamine (glycine max receptors) in ocular tissues. Strong fluorescence* ■. *Moderate fluorescence* ●. *Weak fluorescence* ▲.

react with the lectin under study. As the differences in the cell membrane composition of normal and neoplastic tissues are well documented,[16-20] it is possible that neoplastic change in the embryonic retina is associated either with loss of or a modification in the distribution of D-gal NAc. Alternatively there may have been an overall shortening in length of the saccharide sequences in surface glycoproteins of retinoblastoma cells as is known for other malignant cells.[16,20]

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References

1 Crumpton MJ, Owens RJ, Gallagher CJ, Davies AA. The cell surface and its metabolism. *J Pathol* 1983; **141:** 235–48.

2 Stoddart RW, Collins RD, Jacobson W. Lectin staining of carbohydrates of haemic cell. *J Pathol* 1980; **313:** 321–32.

3 Buck CA, Fuhrer JP, Soslau G, Warren L. Membrane-glycopeptides from subcellular fractions of control and virus-transformed cells. *J Biol Chem* 1974; **249:** 1541–50.

4 Bhavanandan VP, Davidson EC. Mucopolysaccharides associated with nuclei of cultured mammalian cells. *Proc Natl Acad Sci USA* 1975; **726:** 2032–6.

5 Leblond CP. Distribution of periodic acid-reactive carbohydrates in the adult rat. *J Anat* 1950; **86:** 1–8.

6 Liener IE, Wada S. Chemical composition and end groups of the soybean haemagglutinin. *J Biol Chem* 1958; **233:** 395–402.

7 Spiro RG. Glycoproteins: structure, metabolism and biology *N Engl J Med* 1963; **269:** 566–71.

8 Steinemann A, Stryer L. Accessibility of the carbohydrate moiety of rhodopsin. *Biochemistry* 1973; **12:** 1499–506.

9 Moore JC, Tiffany JM. Human ocular mucus origins and preliminary characterisation *Exp Eye Res* 1979; **29:** 291–301.

10 Nir I. Visualization of intracellular concanavalin A binding sites in retinal photoreceptors. *J Histochem Cytochem* 1978; **26:** 822–8.

11 O'Brien BJ. Rhodopsin as a glycoprotein, a possible role for the oligosaccharide in phagocytosis. *Exp Eye Res* 1983; **23:** 127–37.

12 Plantner JJ, Kean EL. Carbohydrate composition of bovine rhodopsin. *J Biol Chem* 1976; **251:** 1548–59.

13 Uehara F, Samesharina M, Takashi M, Ohba N. Localization of fluorescence-labelled lectin binding sites on photoreceptor cells of the monkey retina. *Exp Eye Res* 1983; **36:** 113–23.

14 Zimmerman LE, Eastham AB. Acid mucopolysaccharide in the retinal pigment epithelium and visual cell layer. *Am J Ophthalmol* 1959; **47:** 488–99.

15 McLaughlin BJ, Wood JG. The localization of lectin binding sites on photoreceptor outer segments and pigment epithelium of dystrophic retinas. *Invest Ophthalmol Visual Sci* 1980; **19:** 728–42.

16 Sela BA, Lis H, Sharon N, Sachs L. Different locations of carbohydrate-containing sites in the surface membrane of normal

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and transformed mammalian cells. *J Membr Biol* 1970; **3:** 267–79.

17 Stoddart RW, Collins RD, Jacobson W. The microanalysis of saccharide structures of normal and neoplastic tissues. *Biochem Soc Trans* 1974; **2:** 481–3.

18 Warren L. The malignant cell and its membranes. *Ann J Pathol* 1974; **77:** 69–76.

19 Goldberg AH, Yeoman LG, Busch H. Chromatin-associated glycoproteins of normal rat liver and Novikoff hepatoma ascites cells. *Cancer Res* 1978; **38:** 1052–8.

20 Nicolson GL, Blaustein J. The interaction of *Ricinus communis* agglutinin with normal and tumour cell surfaces. *Biochem Biophys Acta* 1972; **266:** 543–7.

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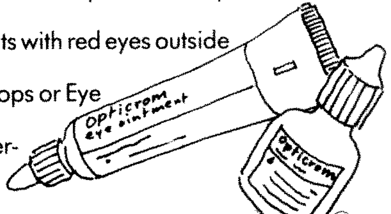

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References: 1. Riddington, C., 'A survey of non-seasonal conjunctivitis' 1982 (data on file).
2. Hennawi, M., British Journal of Opthalmology, 1980, 64, 483-486.

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Assessment of immunological techniques in the diagnosis and prognosis of ocular malignant melanoma

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SUMMARY Tests of cell mediated immunity (one and two stage leucocyte migration inhibition assays) and humoural immunity (membrane immunofluorescence and serum effects on leucocyte migration) were done with leucocytes and sera from 36 patients with uveal melanoma, five with conjunctival melanoma, 21 with non-malignant ocular disease, and 189 with cutaneous melanoma. Cell mediated reactivity with melanoma extracts and serum reactivity with cultured melanoma cells were significantly more frequent in the melanoma patients, but control donor reactivity was also relatively high. Maximum reactivity was found with cells or serum from those patients in whom, on pathological examination, the intraocular melanoma had penetrated the sclera and in patients with conjunctival melanoma. Maximum separation of melanoma patients from control donors was achieved by consideration of the results of several tests done simultaneously. These immunopathological studies were made during the period from 1972 to 1978. At follow-up in 1983 four of the five patients suffering from conjunctival melanoma had died from metastases, and 10 of the 36 with uveal melanoma had died from metastatic disease. The immunological reactions, while of some value in separating melanoma patients from those without melanoma, did not predict whether a particular patient with uveal melanoma would die of metastatic disease or would survive.

In eyes with clear media malignant melanoma of the uveal tract seldom presents a significant diagnostic problem. This is because of the application of supplementary techniques such as ^{32}P uptake, fluorescein angiography, and ultrasonography.[1 2] However, with opaque media, and occasionally even with clear media, assessment of a possible tumour may remain difficult. Current and fundamental problems include a basic lack of understanding of the factors that govern the biological behaviour of ocular melanoma. In particular there is no possibility of our being able to assess the chances of long-term survival for the *individual* patient, though statistical analysis of large numbers of enucleated eyes has emphasised the importance in prognosis of factors such as tumour size, cell type, and the presence or absence of extraocular spread at enucleation.[3] A factor to be taken into account when the nature and mechanisms of metastatic disease are under consideration is the host-tumour relationship. This is also relevant to the therapeutic techniques currently under investigation (local excision, irradiation modes of various types, light and laser coagulation etc.).[1 2]

The immune status of patients with uveal melanoma has been the subject of intensive research for some 15 years,[4] and studies of humoural immunity or cell mediated immunity have shown that in a significant proportion of patients with uveal melanoma there is in-vitro evidence of tumour related immune reactivity.

However, similar in-vitro tests also show immune reactivity to melanoma antigens in a smaller percentage of control patients. In an attempt to refine immunopathological investigations we correlated simultaneous tests of humoural and cell mediated immunity in 36 patients with uveal melanoma and five patients with conjunctival melanoma during the period 1972–8. The results are presented in relation to the pathological findings and survival data for patients over not less than five years. The results from ocular melanoma patients are compared with data compiled for patients with cutaneous melanoma.

Correspondence to Alistair J Cochran, MD.

Patients and materials

Leucocytes and serum were available from 41 patients (27 f, 14 m) with malignant melanoma of the eye and 21 patients with non-malignant ocular conditions. The melanoma was in the choroid of 30 patients, in the ciliary body or iris in six patients, and on the conjunctiva in five patients. The clinical details and pathological diagnoses were not known to the people undertaking the immunological studies at the time they did them.

Blood samples were also obtained from 120 patients with cutaneous melanoma and 153 with non-melanomatous malignancy or non-malignant conditions. This material has been described in detail elsewhere.[5]

Assessment of cell mediated immunity. This was examined (1) by a one-stage capillary leucocyte migration assay modified from the technique of Bendixen and Søborg[6] and described by Ross *et al.*,[7] and (2) by a two-stage lymphokine generation assay using normal human peripheral blood leucocytes as indicator cells.[8]

Blocking activity in the patients' sera and inherent serum inhibitory activity were examined by a modification of the capillary leucocyte migration assay.[9] Humoural immunity was tested by an indirect membrane immunofluorescent technique employing monolayers of malignant melanoma cells grown on flying coverslips in Leighton tubes.

OCULAR PATHOLOGY

Excised globes or tumour tissues were fixed in 2% glutaraldehyde and processed through paraffin. Sections from several blocks from each tumour were cut at 6–8 μm and stained with haematoxylin and eosin, reticulin (Gordon and Sweet), and Masson Fontana for melanin.

During the macroscopic examination of excised globes the eyes were examined for extraocular extension, and the vortex veins were removed for separate histological examination. Evidence of trans-scleral or episcleral tumour extension was looked for, and appropriate blocks were taken for histological confirmation. Approximate tumour volume was calculated by measuring the tumour diameter (d) in three planes and applying the formula:

$$V = \frac{4}{3}\pi \left(\frac{d^1}{2} \times \frac{d^2}{2} \times \frac{d^3}{2}\right).$$

Statistical analysis. Reaction frequencies in the different subgroups were compared by the χ^2 test with Yates's correction for small numbers where appropriate. The difference between two groups was accepted as significant when p was less than 0·05.

Results

The data were analysed for melanomas arising at different sites within the eyeball and on the conjunctiva (Table 1). A majority of patients reacted (*a*) in the leucocyte migration assay when medium supplemented with fetal calf serum was used to suspend the melanoma antigen and (*b*) in the membrane immunofluorescence test. A smaller but still substantial proportion of patients' leucocytes were inhibited by melanoma antigens suspended in medium supplemented with autologous serum in the leucocyte migration assay. A smaller proportion showed leucocyte migration inhibition in medium supplemented with autologous serum without added melanoma antigen. While reactivity seemed higher in the conjunctival melanoma patients, the number of such patients studied was small.

Reactions of ocular melanoma patients compared with controls. The migration of leucocytes from melanoma patients was frequently inhibited by exposure to formalinised melanoma cells (FMC) in the one-stage capillary migration assay with fetal calf

Table 1 *Immunological reactions of patients with ocular melanomas subdivided by site of primary tumour*

Technique	*Site of melanoma*					
	Choroid		*Ciliary body/iris*		*Conjunctiva*	
	*Positive**		*Positive*		*Positive*	
	Total	*%*	*Total*	*%*	*Total*	*%*
Leucocyte migration FMC in medium with 10% FCS	22/30	73	3/4	75	5/5	100
Leucocyte migration FMC in medium with 10% autologous serum	13/20	65	2/4	50	4/4	100
Leucocyte migration in medium with 10% autologous serum without FMC	5/20	25	1/4	25	2/4	50
Membrane immunofluorescence	16/22	73	3/4	75	3/4	75

*Number of positive tests/total of individuals tested.
FMC=formalinised melanoma cells.

Table 2 *Immunological reaction of patients with ocular or cutaneous melanoma and control donors*

Technique	*Melanoma patients*								*Control donors*			
	All ocular		*Intraocular*		*Conjunctival*		*Cutaneous*		*Ocular*		*Non-ocular*	
	Positive		*Positive*		*Positive*		*Positive*		*Positive*		*Positive*	
	Total	*%*	*Total*	*%*	*Total*	*%*	*Total*	*%*	*Total*	*%*	*Total*	*%*
Leucocyte migration FMC in medium supplemented with fetal calf serum	31/40	78	26/35	74	5/5	100	99/120	83	4/11	36	67/189	35
Leucocyte migration FMC in medium supplemented with autologous serum	19/32	59	15/28	54	4/4	100	39/71	55	3/9	33	4/43	9
Leucocyte migration in medium with autologous serum without FMC	13/41	32	11/37	30	2/4	50	42/89	48	4/21	19	14/100	14
Membrane immunofluorescence	25/34	74	22/30	73	3/4	75	48/83	58	4/11	36	13/57	23
Two-stage assay	3/9	33	3/9	33	NT	NT	31/65	48	NT	NT	5/38	13

NT=not tested.

serum as the additive (Table 2). The frequency of inhibition (31 out of 40, 78%) is similar to that observed in patients with cutaneous melanoma (83%). In comparable experiments the leucocytes of ocular disease control donors (4 out of 11, 36%) and of other control donors (67 out of 189, 35%) were significantly less frequently inhibited ($p<0{\cdot}005$ in both cases). When autologous serum (AS) was substituted for fetal calf serum in the migration medium, melanoma patients' leucocytes were inhibited significantly more frequently (ocular 19 out of 32, 59%); cutaneous 39 out of 71, 55%) than leucocytes from non-ocular control donors (4 out of 43, 9%—$p<0{\cdot}05$). In a small group of ocular control donors leucocyte inhibition in medium supplemented with AS was not significantly less frequent (3 out of 9, 33%) than that observed with the melanoma patients (19 out of 32, 59%).

When leucocytes were exposed to AS without the addition of FMC, uveal melanoma patients' leucocytes were inhibited moderately frequently (13 out of 41, 32%), a rate that did not differ significantly from that of cutaneous melanoma patients (42 out of 89, 48%) or ocular controls (4 out of 21, 19%), though non-ocular controls (14 out of 100, 14%—$p<0{\cdot}025$) reacted significantly less frequently.

Uveal melanoma patients were tested in a two-stage assay, and although the frequency of reaction (3 out of 9, 33%) was higher than that observed with non-ocular control donors (5 out of 38, 13%—NS), it was significantly lower than that observed with cutaneous melanoma (31 out of 65, 48%) and with ocular melanoma patients in the one-stage assay ($p<0{\cdot}05$).

In a study of humoural immunity employing membrane immunofluorescence of monolayer tissue cultures of cutaneous melanoma cells 25 out of 34 ocular melanoma patients tested (74%) gave a positive reaction, a frequency similar to that of cutaneous melanoma patients (48 out of 83, 58%) but significantly higher than that of ocular controls (4 out of 11, 36%—$p<0{\cdot}05$) or non-ocular controls[5] (13 out of 57, 23%—$p<0{\cdot}001$).

Patient reactivity related to clinical stage. This was considered from two standpoints. First, we considered patients who showed distant spread of their tumour. At the time of testing, only three patients had spread of disease beyond the primary ocular site, in each case by haematogenous spread to remote viscera. Only one of these patients showed a positive reaction to FMC in the leucocyte migration assay (in the presence of FCS). The other assays were done on only one patient and were all negative.

The second aspect of stage of tumour progression considered was microscopic evidence of local extraocular extension (that is, trans-scleral, episcleral, or orbital tumour) (Table 3). Regardless of the immunological technique employed the reaction frequency of patients with evidence of extraocular extension was higher than that of patients in whom the tumour was confined to the globe. The differences were statistically significant with the exception of those observed with the leucocyte migration assay in the presence of autologous serum.

Follow-up of the patients in this study to 1983, five years or more, has shown that four of five with conjunctival melanoma and 10 of 36 with intraocular melanoma died from metastatic melanoma. The pattern of immunological tests did not have significant characteristics in the individual patients who subsequently died from metastases.

Correlation of immunological reactivity of patients

Table 3 *Reaction of uveal melanoma patients with melanoma cells, related to presence or absence of histological evidence of local extraocular spread. Data only from patients whose eye specimens were available for histological study in Glasgow are presented*

Technique	*Intra- or episcleral spread*				
	Yes		*No*		
	Patients		*Patients*		*p*
	Total	*%*	*Total*	*%*	
Leucocyte migration FMC in medium with 10% FCS	8/8	100	10/16	63	<0·05
Leucocyte migration FMC in medium with 10% autologous serum	4/6	67	7/15	47	>0·50
Leucocyte migration in medium with 10% autologous serum without FMC	5/8	63	4/20	20	<0·05
Membrane immunofluorescence	7/7	100	10/19	53	<0·05

with ocular malignant melanoma and the histological features of their tumours. We related the presence or absence of reactivity in the immunological tests to conventional histological and cytological features of the patients' tumours: spindle or epithelioid cell cytology, the degree of melanogenesis, mitotic rate, and presence and extent of lymphocytic infiltration. We found no significant correlation between the various histological criteria and immunological reactivity and non-reactivity.

Discrimination between patients with uveal melanoma and those with other ocular diseases on the basis of the number of positive tests. A comparison of uveal melanoma patients and control donors showed that a higher proportion of the tumour patients reacted positively in the leucocyte migration assay in the presence of tumour antigen, in the membrane immunofluorescence test, and in the assay studying the effect of autologous serum on leucocyte migration in the absence of added antigen (Table 4). A relatively high proportion of the ocular control donors also reacted, especially in the first two tests. We therefore combined the patterns of reaction in the different tests in various ways to see whether this would better separate the two populations and provide a more specific indication of the presence of ocular melanoma. This was achieved when we compared those who reacted in two or three tests. However, with three tests the absolute proportion of ocular melanoma patients who reacted dropped to an unacceptably low 31%. When we combined reactivity in the leucocyte migration assay in the presence of antigen and in the immunofluorescence technique, we found that 56% of ocular melanoma patients reacted in both tests, whereas only one of nine (11%) of the ocular controls reacted in both. This was the optimum combination of tests that minimised 'false positive' reactions in controls.

Table 4 *Discrimination between patients with ocular melanoma and those with other ocular diseases on the basis of number of tests done*

Number of tests	*Patients with intraocular melanoma*		*Ocular controls*	
	Positive		*Positive*	
	Total	*%*	*Total*	*%*
One test positive (A)	26/35	74	4/11	36
One test positive (B)	22/30	73	4/11	36
One test positive (C)	11/37	30	4/21	19
Two tests positive (A+B)	16/30	53	1/9	11
Three tests positive (A+B+C)	9/29	31	1/9	11

A=Leucocyte migration inhibitions by melanoma cells in fetal calf serum or autologous serum. B=Membrane immunofluorescence *vs* cultured melanoma cells. C=Leucocyte migration inhibition by autologous serum in the absence of added tumour antigen.

Discussion

There is now considerable evidence that in-vitro tests show tumour-directed antibodies in the serum of patients with uveal or conjunctival melanoma. The percentage of patients with such antibodies in our series (25 out of 34, 73%) compares favourably with the 78% (57 out of 73) reported by Felberg *et al.*[10] The complexity of the immunocytochemical problems in the assessment of tumour antigenicity was described by Rahi[11] in 1971, and it is not surprising that there has been variation in results from different centres. The detection of humoural antibodies to melanoma cells has been confounded by cross-reactivity, for example the presence of antiactin antibodies[12] in melanoma patients and controls. Ostensibly anti-melanoma antibodies were found in our series in four of 11 (36%) ocular controls, but only in four in 33 (12%) of the combined skin and uveal controls. This is similar to the false positive rate reported by Felberg *et al.*[10] (25 out of 106, 24%). However, modification of the immunofluorescence technique by absorption has significantly improved specificity.[13]

In-vitro tests of cell mediated immunity in uveal melanoma show variable results when antigens are obtained from different ocular melanomas.[14, 15] This is probably the main reason for the lack of consistency shown by different studies carried out to date.

We have examined the usefulness of combinations of various in-vitro immunological tests to discriminate between patients with malignant melanomas, patients with non-malignant ocular conditions, and normal people without clinically apparent ocular disease.

In assessing individual tests we found that all were more often positive in patients with ocular melanoma than in the control groups. The high frequency of reaction of the ocular melanoma patients in both the one-stage leucocyte migration assay against melanoma-associated antigens and the membrane immunofluorescence technique is encouraging. However, there was also a comparatively high frequency of reaction in control donors, particularly the ocular control donors, in these tests. Discrimination is considerably improved when we assess the concurrence of positive results in the leucocyte migration assay and the membrane immunofluorescence test done simultaneously. This gave excellent separation of ocular melanoma patients and the control donors, but unfortunately the absolute frequency of reaction in the melanoma group dropped to 53% compared with 11% in the control group. Thus with refinements in technique there is some prospect of an immunological profile being of diagnostic value in patients who have opaque media or a questionable diagnosis.

Little difference was found between groups of people subdivided by sex, site of primary tumour, and gross and microscopic features of the tumours, and this supports previous findings.[16-18] A striking exception is the fact that patients whose tumours showed transcleral and episcleral extension were very much more often reactive than patients whose tumours were confined to the globe. This finding is in keeping with the view that the interior of the eye is to some extent an immunologically privileged site and suggests that the autoimmunising capacity of the cells of an ocular malignant melanoma is greatly increased once these cells penetrate beyond the sclera.[19] The failure of the tests to provide prognostic indicators was disappointing, as no correlation was found with survival rate.

In summary the studies undertaken support previous reports of autoimmunogenic tumour-associated antigens on malignant melanomas in general and ocular malignant melanomas in particular. In our view the tests are not at present applicable in a routine fashion as diagnostic or prognostic aids in malignant melanoma. This opinion is based on the technical complexity of tests employed and also the high levels of false positivity and false negativity. We therefore require more refined tests that can be applied on a large scale and which would have a markedly higher rate of reaction within the melanoma patients and a considerably lower reaction frequency in the control donors. False positive results suggest that inflammation or other non-tumorous processes may lead to transient immune responses. Further purification of ocular melanoma antigens and sequential studies may assist in refining the specificity of the tests employed, and perhaps access to free antigen in the *aqueous* humour might produce a more reliable source of information.

References

1 Foulds WS. Ocular melanoma. In: McKie RM ed. *Pigment cell.* Basel: Karger, 1983; **6:** 127–49.

2 Shields JA. *Diagnosis and management of intraocular tumours.* St Louis: Mosby, 1983.

3 Thomas JV, Green WR. Melanotic uveal tumours. In: Garner A, Klintworth GK, eds. *Pathobiology of ocular disease.* New York: Dekker, 1983: 651–88.

4 Rahi AHS. Immunology of ocular tumours. In: Garner A, Klintworth GK, eds. *Pathobiology of ocular disease.* New York: Dekker, 1983: 823–42.

5 Cochran AJ. *Man cancer and immunity.* London: Academic Press, 1978.

6 Bendixen G, Søborg M. A leucocyte migration technique for in vitro detection of cellular (delayed type) hypersensitivity in man. *Dan Med Bull* 1969; **16:** 1–6.

7 Ross CE, Cochran AJ, Hoyle DE, Grant RM, McKie RM. Formalised tumour cells in the leucocyte migration inhibition test. *Clin Exp Immunol* 1975; **22:** 126–32.

8 Morrison LJ, Cochran AJ, McKie RM, Ross CE, Todd G, Garland C. A study of patients with malignant melanoma using an indirect leucocyte migration assay. *Int J Cancer* 1979; **21:** 11–6.

9 Cochran AJ, McKie RM, Ross CE, Ogg LJ, Jackson AM. Leucocyte migration inhibition by cancer patients sera. *Int J Cancer* 1976; **18:** 274–81.

10 Felberg NT, Pro-Landazuri JM, Shields JA, Federman JL. Tumour-associated antibodies in the serum of patients with ocular melanoma III. Immunoperoxidase detection. *Arch Ophthalmol* 1979; **97:** 256–9.

11 Rahi AHS. Autoimmune reactions in uveal melanoma. *Br J Ophthalmol* 1971; **55:** 793–807.

12 Malaty AHA, Rahi AHS, Garner A. Ostensible anti melanoma antibodies in patients with non-malignant eye disease. In: Silverstein AM, O'Connor GR, eds. *Immunology and immunopathology of the eye.* New York: Masson, 1979: 216-22.

13 Felberg NT, Donoso LA, Federman JL. Tumour-associated antibodies in the serum of patients with ocular melanoma. IV Correction for smooth muscle antibodies. *Ophthalmology* 1980; **87:** 529–33.

14 Char DH, Jerome L, McCoy JL, Herberman RB. Cell-mediated immunity to melanoma-associated antigens in patients with ocular malignant melanoma. *Am J Ophthalmol* 1975; **79:** 812–6.

15 Manor RS, Livni E, Joshua H, Ben-Sira I. Inhibition of macrophage migration by choroidal malignant melanoma-associated antigens in patients with uveal melanoma. *Invest Ophthalmol Visual Sci* 1978; **17:** 684–7.

16 Char DH. Inhibition of leukocyte migration with melanoma-associated antigens in choroidal tumours. *Invest Ophthalmol Visual Sci* 1977; **16:** 176–9.

17 Felberg NT, Federman JL, Shields JA, Michelson JB. Tumour-associated antibodies in patients with ocular melanoma. In: Silverstein AM, O'Connor GR eds. *Immunology and immunopathology of the eye.* New York: Masson, 1979: 202–8.

18 Kalafut F, Gernak A, Pham Manh Hung. Detection of specific immunoreactivity by LAI assay in patients with malig-

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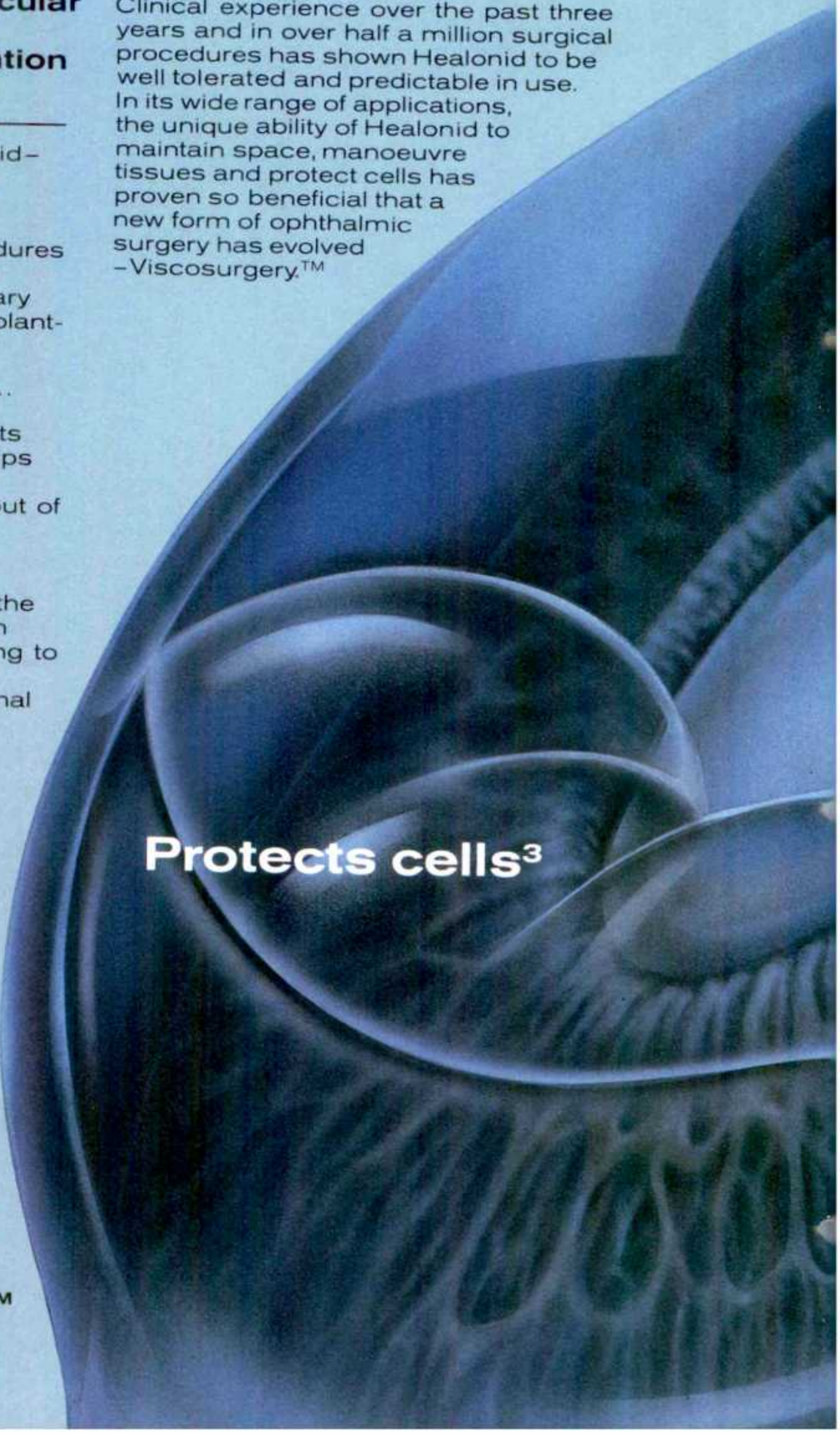

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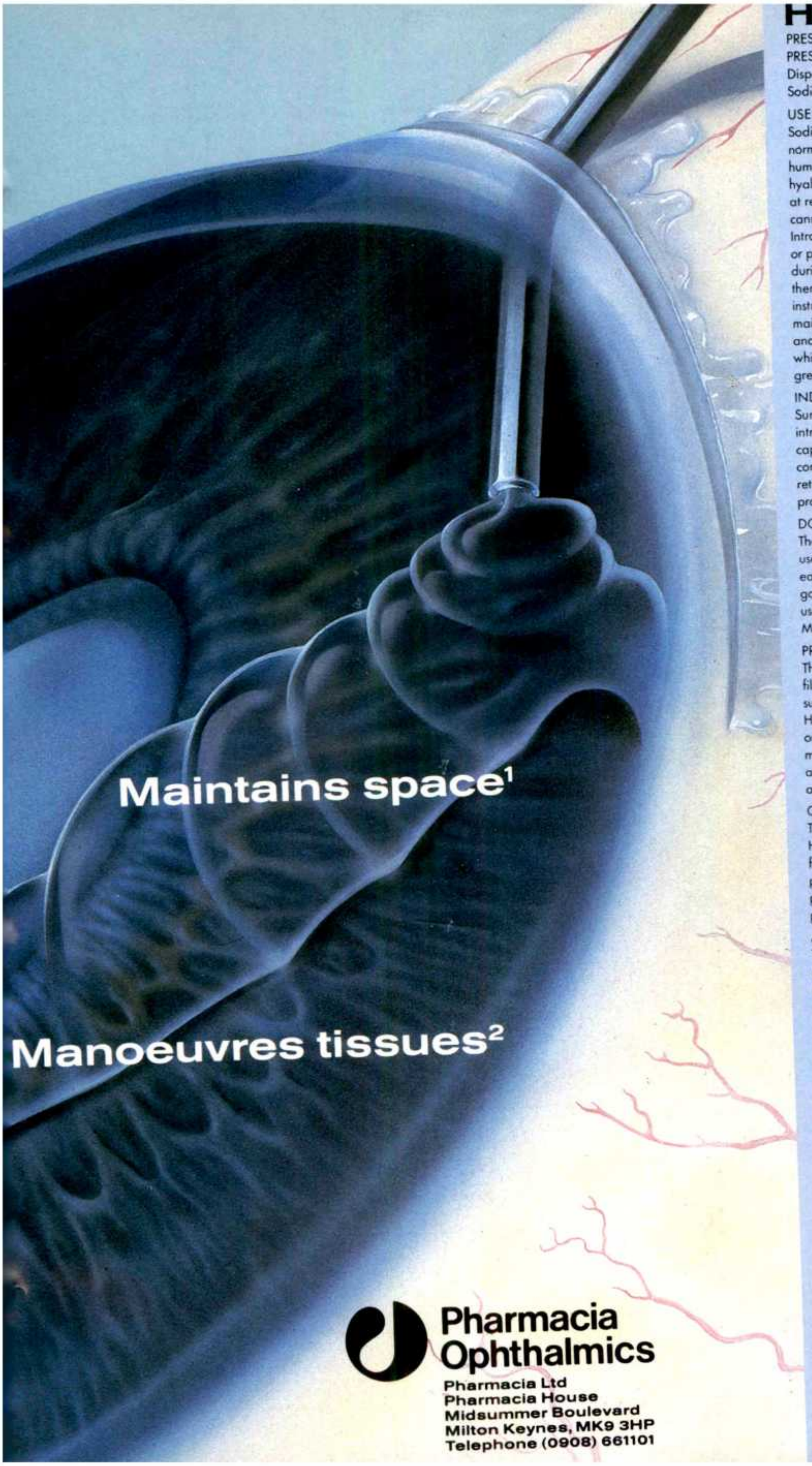

Healonid

PRESCRIBING TABLE

PRESENTATION
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USES
Sodium hyaluronate is a visco-elastic polymer normally found in the aqueous and vitreous humour. HEALONID, which contains sodium hyaluronate is a highly viscous clear solution at rest, yet it will readily flow through a fine cannula or needle under pressure.
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INDICATIONS
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DOSAGE AND ADMINISTRATION
The syringe is assembled and made ready for use according to the instruction sheet with each syringe. The indication for use will govern the timing and quantity of HEALONID used. See data sheet for Healonid Monograph.

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PHARMACEUTICAL PRECAUTIONS
Store at 2-8°C protected from light and freezing. Shelf life 3 years.

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British Journal of Ophthalmology, 1985, **69**, 177–179

Pre-enucleation irradiation of uveal melanoma

DEVRON H CHAR AND THEODORE L PHILLIPS

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SUMMARY The relative efficacy of various types of treatment in preventing metastatic uveal melanoma is unclear. We have performed a phase I-II non-randomised trial to determine if patients with large (>15 mm in diameter or > 5 mm in thickness) uveal melanomas would benefit from pre-enucleation irradiation. Twenty-eight patients were treated between 1978 and 1983 by means of 5×5 cm anterior wedge pair ports on a 4 me V linear accelerator. Each patient received five 4 gray (400 rad) fractions over a five-day period for a total of 20 Gy. Enucleation was performed by a single surgeon within five days after treatment. The mean follow-up of the patients was 24 months (range 7-54 months). All melanomas were histologically confirmed. Four patients (14%) have developed metastic tumour with a mean interval between diagnosis and death of 25 months. No significant perioperative or long-term morbidity was observed.

There are some unresolved issues in the management of uveal melanoma. The relative efficacy of various types of treatment in preventing metastases is unclear. Some investigators have shown that patients treated by, variously, photocoagulation, radioactive plaques, and charged particle irradiation as alternatives to enucleation have a relatively low incidence of uveal melanoma metastases, but data from randomised prospective treatment trials are lacking.[1-3] Some authors have compared their results either with those from historic controls or with those from intra-institution non-randomised patients treated with alternative therapy or enucleation.[3 4] Either method of comparison may be inaccurate. Changes in the definition of melanoma size have been made, and it is not clear what criteria were used to select alternative therapy versus enucleation in non-randomised studies from a single institution. The incidence of distant metastases may be changing as earlier diagnoses are made.

About five years ago we began a phase I-II non-randomised trial to determine if uveal melanoma patients with tumours greater than 15 mm in diameter or greater than 5 mm in thickness would benefit from pre-enucleation irradiation. In some cases of systemic malignancy preoperative irradiation was associated with decreased tumour-related mortality, and our initial investigation was a pilot study of morbidity and mortality prior to a randomised prospective national trial to determine if pre-enucleation irradiation in cases of poor-risk uveal melanoma might decrease tumour-related mortality.[5] This report presents our preliminary data. The relatively low incidence of short-term metastatic disease demonstrates the need for a randomised prospective study to determine what is the optimal therapy for patients with uveal melanomas.

Materials and methods

All patients were examined in the Ocular Oncology Unit, University of California, San Francisco between 1978 and 1983. The diagnosis of uveal melanoma was confirmed on the basis of clinical, ultrasonographic, photographic, and fluorescein angiographic criteria prior to therapy. Written and oral informed consent was obtained in all cases. Patients had a thorough physical examination, serum liver function tests (lactic dehydrogenase, alkaline phosphatase, and SGOT), and postero-anterior and lateral chest *x*-rays to detect possible metastases. If abnormalities were observed in any of these tests, a further examination was carried out.[6]

Pre-enucleation irradiation was performed on a 4 me V linear accelerator with 5×5 cm anterior wedge pair ports. All patients received five 4 gray (Gy) (400 rad) fractions of 4 meV photon irradiation on five consecutive days for a total of 20 Gy, and enucleation was performed by a single surgeon (D.H.C.) within five days after cessation of radiation

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therapy. Enucleation was performed in a standard manner without cryoprobe, aqueous paracentesis, or other ancillary 'minimal touch enucleation manoeuvers.'

Tumour sizes were measured initially by clinical examination and both immersion B-scan and quantatitive A-scan ultrasound. Tumour dimensions were confirmed both at the time of surgery, by corneal transillumination, and when eyes were examined in the eye pathology laboratory. All eyes were examined histologically and contained uveal melanomas; the tumours' cell types were classified in the standard manner.[7] As outlined above, all patients have had serial evaluations for metastatic disease every three months.

Results

Twenty-eight patients with large (>15 mm in diameter or >5 mm in thickness) uveal melanomas received 20 Gy of conventional photon pre-enucleation irradiation. After a standard enucleation they have been serially followed up for 7-54 months (mean 24 months). No patients have been lost to follow-up.

All melanomas were examined and the diagnosis confirmed histologically. Six patients had spindle B tumours, 14 had mixed tumours with predominantly spindle B cells, six patients had mixed tumours, one patient had an epithelioid, and one a necrotic melanoma. No eyes had histological evidence of extraocular extension.

Four patients (14%) have developed metastatic melanomas, and these have been confirmed histologically. All four have died from metastases, death occurring 19-30 months (mean 25 months) after treatment.

No significant perioperative or long-term morbidity beyond that seen with standard enucleation was observed after this dose of pre-enucleation irradiation.

Discussion

We have demonstrated that pre-enucleation irradiation using five 4 Gy fractions can be performed with minimal perioperative or long-term morbidity. Less than 0·2 Gy is delivered to the contralateral lens, and we have observed no contralateral ocular, prosthesis/implant, or other cranial problems as a result of this adjunct therapy. Secondly, we have demonstrated that the short-term melanoma-related mortality in these treated patients with currently defined large melanomas is relatively low. Only four of 28 patients (14%) developed metastases; however, the five-year metastatic rate will undoubtedly be higher.

The observation of lower than expected mortality in patients with large uveal melanomas treated by pre-enucleation irradiation may have several possible explanations. First, it suggests to us that the use of historic controls is inappropriate; some investigators have stated that large uveal melanomas have a five-year tumour-related mortality approaching 40%, but this level may no longer be correct. Secondly, it demonstrates the need for prospective randomised treatment trials to determine the relative efficacy of different forms of therapy in the prevention of uveal melanoma metastases, and to establish the metastasis rate for present day patients. Thirdly, it leads us to believe that pre-enucleation irradiation may have an effect on tumour mortality, and that it would be reasonable to mount a prospective national randomised study of this approach.

The objective of a randomised pre-enucleation irradiation study is to determine whether pre-enucleation irradiation at this dose and fractionation schedule would decrease the prevalence of metastases in patients with large (>15 mm diameter or >5 mm thickness) uveal melanomas.

There are several potential limitations. If patients with uveal melanoma develop only micrometastases prior to ocular treatment, this therapeutic approach would be ineffective. Secondly, most tumours in which pre- or perioperative irradiation has been successful have been those which have a propensity for local spread and involvement of regional lymph nodes; this is not the case for uveal melanomas.[8-10] Thirdly, it is possible that the dose or fractionation schedule used in this study is not optimal.

The radiation parameters chosen for this study were based on four considerations. First, in some previous studies of other tumour sites this radiation dose has been effective.[8-10] Secondly, melanomas may be more susceptible to high (4 Gy) than conventional (2 Gy) fractions.[5] Thirdly, at this dose out-of-town patients can be treated in a timely manner; markedly to increase the radiation dose by conventional fractions would necessitate four to five weeks of therapy. Fourthly, this relatively low dose can be delivered safely and has a lower potential for untoward side effects. Fifthly, the rationale is to reduce systemic seeding of viable tumour cells at surgery; this radiation dose should reduce the percentage of viable cells by several log units.

The preliminary results with pre-enucleation irradiation appear promising. A randomised prospective treatment trial is needed. It can be effectively mounted to test the hypothesis within a reasonable length of time.

This work was supported in part by an unrestricted grant from That Man May Sec, and from NIH Research grants EYO3675 and EYO1441. Dr Char is a recipient of the Robert C McCormick scholar award from Research to Prevent Blindness Inc.

References

1 Vogel MH. Treatment of malignant choroidal melanomas with photocoagulation. *Am J Ophthalmol* 1972; **74:** 1-11.

2 Stallard HB. Malignant melanoblastoma of the choroid. *Mod Probl Ophthalmol* 1968; **7:** 16-30.

3 Char DH. Management of small choroidal melanomas. *Surv Ophthalmol* 1978; **22:** 377-86.

4 Gragoudas ES, Goitein M, Verhey L, *et al.* Proton beam irradiation of the uveal melanoma. Results in five and half-year study. *Arch Ophthalmol* 1982; **100:** 928-34.

5 Char DH, Phillips TL. The potential for adjuvant radiotherapy in choroidal melanoma. *Arch Ophthalmol* 1982; **100:** 247-8.

6 Char DH. Metastatic choroidal melanoma. *Am J Ophthalmol* 1978; **86:** 76-80.

7 Char DH, Stone RD, Irvine AR, *et al.* Diagnostic modalities in choroidal melanoma: sensitivity, specificity, and reproducibility. *Am J Ophthalmol* 1980; **89:** 223-30.

8 Rider WD, Palmer JA, Mahoney LJ, Robertson CT. Preoperative irradiation in operable cancer of the rectum: Report of the Toronto Trial. *Can J Surg* 1977; **20:** 335-8.

9 Miller LF. Bladder cancer. Superiority of preoperative irradiation and cystectomy in clinical stages B_2 and C. *Cancer* 1977; **39:** 973-80.

10 Stevens KR Jr, Allen CV, Fletcher WS. Preoperative radiotherapy for adenocarcinoma of the rectosigmoid. *Cancer* 1976; **37:** 2866-74.

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Malignant melanoma of the eyelid skin: histopathology and behaviour

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SUMMARY Histological sections from 24 patients with malignant melanoma of the eyelid skin were studied and correlated with clinical follow-up for an average of 8·6 years. There was an average post-treatment follow-up of 7·4 years with a cure rate of 78% in the superficial spreading group. The average follow-up in the nodular melanoma group was 9·4 years with a cure rate of 75%. Nodular melanoma patients with the lesion in the lid margin have a worse prognosis than those with the lesion on the eyelid skin.

Malignant melanoma of the eyelids, apart from the conjunctival surface, accounts for about 1% of all eyelid tumours[1] and slightly less than 7% of cutaneous malignant melanoma in the head and neck region.[2] Because of its rarity descriptions have been based on the study of small groups or isolated cases, and it has been difficult to establish a comprehensive and representative picture of the histology and behaviour of malignant melanoma in this situation. In the following account we describe the prognosis and histopathology in 24 patients followed up for between three and 33 years.

Patients and methods

A total of 24 patients, for whom adequate follow-up information was available, were included in the series. Their ages ranged from 18 to 80 years, with a majority presenting in the 6th and 7th decades. Females (15) were affected slightly more commonly than males (9). More than half of the tumours were located on the eyelid margin, and a further half of these were unpigmented. The upper lid was affected in 16 patients the lower lid in eight. The distribution was equal in the medial and lateral areas of the eyelids. Although it was not possible to comment on the clinical presentation of the tumours because of the retrospective nature of the majority in this study, 25% of the patients were seen preoperatively by one of the authors (RC). Patients who presented clinically with a flat lesion (Fig. 1) were most likely to have a superficial spreading malignant melanoma than were patients presenting with a bulky or marginal lesion (Fig. 2), who were more likely to have a nodular melanoma.

In our series 21 patients had surgery, two had irradiation, and one both treatments.

The type of surgery varied with the size of the lesion. The margins of the excised specimens were histologically clear in 22 patients. In two patients in whom clearance was incomplete a second surgical procedure was performed with complete removal of

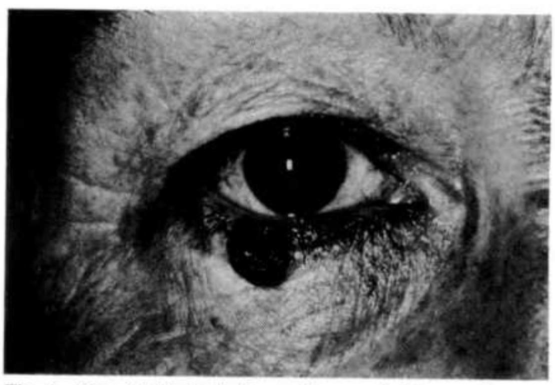

Fig. 1 *Case 8. Clinical picture of a superficial spreading malignant melanoma.*

Correspondence to Professor A Garner.

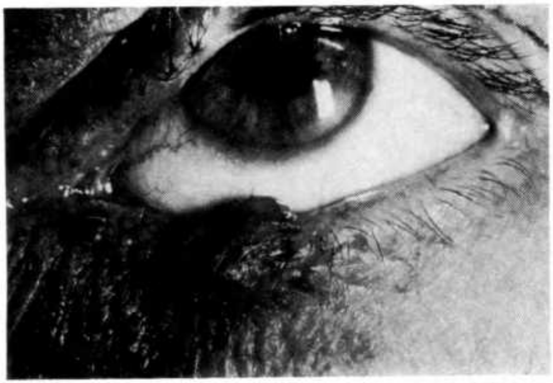

Fig. 2 *Clinical appearance of an unpigmented nodular melanoma of lid margin.*

the residual tumour. No figures are available on the number of patients who were subjected to a diagnostic as opposed to an excisional biopsy.

Histological sections were examined from each of the 24 patients. The sections were drawn from the files of the Institute of Ophthalmology, London (21 cases), the Dutch Cancer Institute at the Antoni van Leeuwenhoek Ziekenhuis (two cases), and the Royal Marsden Hospital, London (one case). Representative haematoxylin and eosin stained sections, including bleached preparations, were reviewed by two of the authors (AG and AL) using diagnostic criteria as defined by Levene.[3] Three categories of invasive melanoma were recognised for the purpose of classification: lentigo maligna melanoma, superficial spreading malignant melanoma, and nodular malignant melanoma.[4 5]

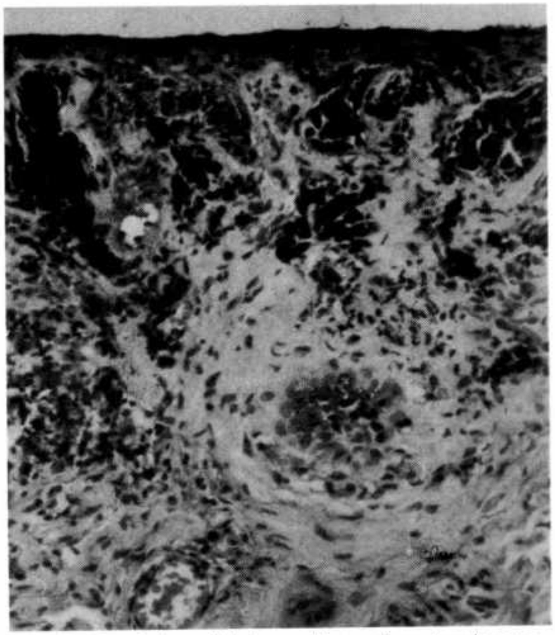

Fig. 3 *Case 3. Superficial spreading malignant melanoma. Invasion by heavily pigmented, pleomorphic tumour cells is confined to the epidermis and superficial stroma. (Haematoxylin and eosin, ×160).*

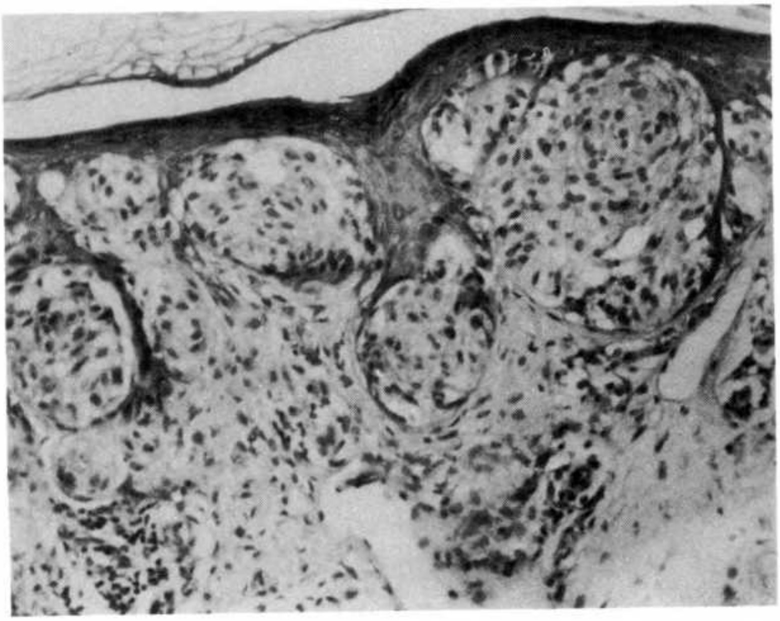

Fig. 4 *Case 6. Superficial spreading malignant melanoma. The epidermis is infiltrated by clusters of lightly pigmented melanocytes with minor invasion of the dermis. (Haematoxylin and eosin, ×160).*

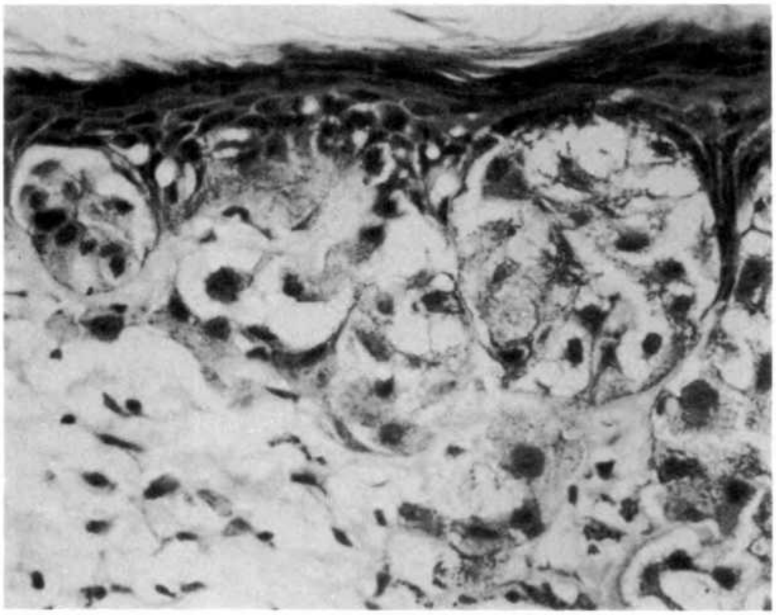

Fig. 5 *Case 3. Superficial spreading malignant melanoma. The epidermis is infiltrated and partially destroyed by groups of tumour cells that have abundant cytoplasm containing fine melanin granules. (Haematoxylin and eosin, ×400).*

Results

HISTOPATHOLOGY

Superficial spreading malignant melanoma was diagnosed in nine cases on the basis of intraepidermal invasion not confined to the basal layer by cells with appreciable cytoplasm containing, in all but one instance, a light dusting with melanin (Figs. 3–5). There was variable stromal invasion, and the maximum thickness of the tumour ranged from 0·1 to

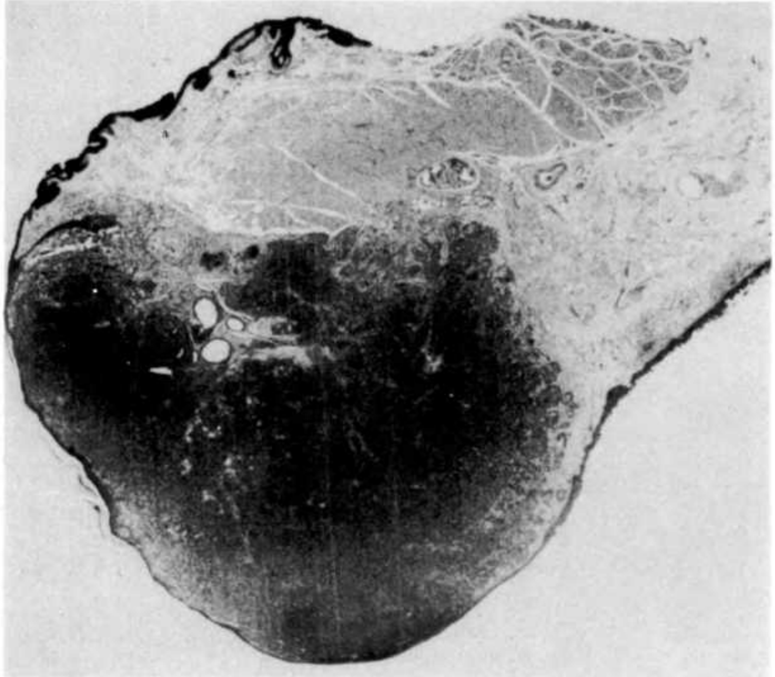

Fig. 6 *Case 10. Nodular malignant melanoma. There is minimal lateral spread of a fairly discrete tumour that involves both the conjunctiva and skin at the lid margin. (Haematoxylin and eosin, ×15).*

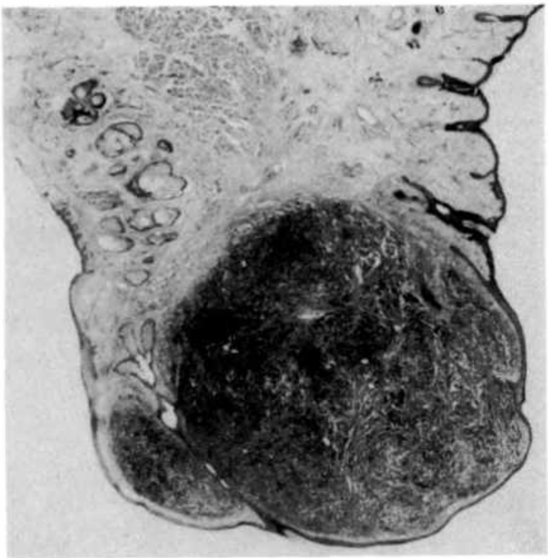

Fig. 7 *Case 12. Nodular malignant melanoma. A well-defined pigmented tumour located at the eyelid margin. (Haematoxylin and eosin, ×14).*

2·2 mm, mean 0·55 mm. In two cases (Nos. 2 and 7) the lesion was essentially in situ with minimal evidence of stromal invasion. Mitotic figures were generally inconspicuous.

In 12 cases the tumour was considered to be a nodular malignant melanoma in that there was extensive invasion of the subepithelial stroma with minimal evidence of junctional activity or lateral intraepidermal spread. The tumour appeared to have arisen in the region of the lid margin in four instances (Nos. 10, 12, 15, and 20) where the epidermis and conjunctival epithelium meet (Figs. 6 and 7). The maximum thickness of the tumours varied considerably, from 1·2 to 3·9 mm (mean 2·38 mm). Cellular pleomorphism with variation in nuclear size, shape, and staining intensity was seen to a greater or lesser extent in all tumours, and in most the nucleoli were moderately or markedly conspicuous (Figs. 8–10). Mitotic figures were observed in all but three cases and in five exceeded an average of two per high-power field. The melanin content was variable, and five of the 12 cases appeared to be amelanotic.

The available sections in three cases were inadequate to allow recognition of the histological type, though the cytological features and evidence of stromal infiltration were such as to justify the diagnosis of malignancy.

No example of lentigo maligna melanoma was recognised.

BEHAVIOUR

Superficial spreading malignant melanoma. Post-treatment follow-up covered an average of 7·4 yr, five of the nine patients being followed up for a minimum of five years. There were two tumour-related deaths, after seven and 12 yr, respectively, both having distant metastases.

Nodular malignant melanoma. The average length of follow-up after treatment of the initial lesion was

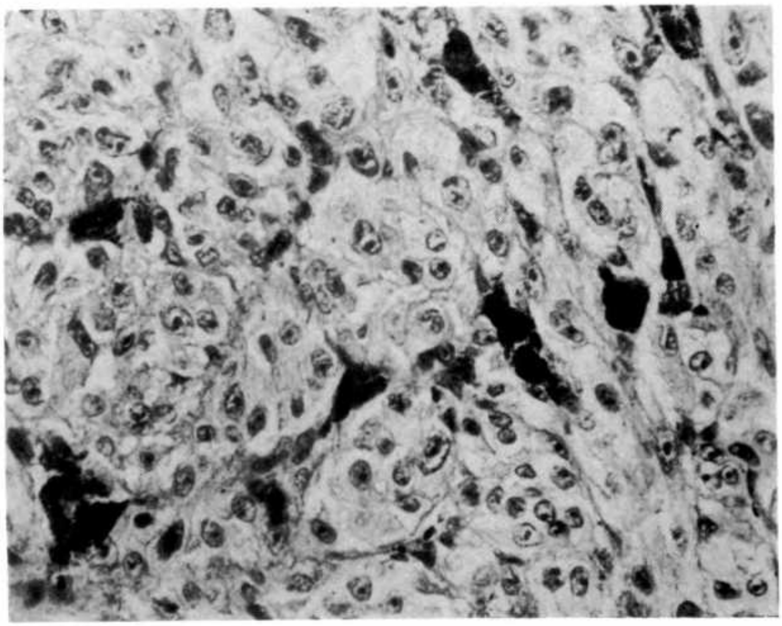

Fig. 8 *Case 11. Nodular malignant melanoma. The tumour cells have generally abundant cytoplasm, contain varying amounts of pigment and conspicuous nucleoli. (Haematoxylin and eosin, ×400).*

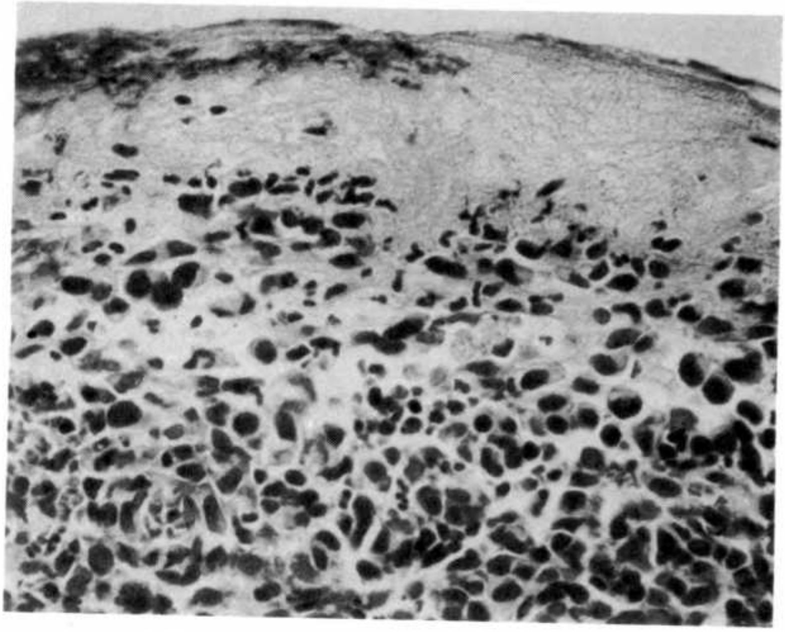

Fig. 9 *Case 13. Nodular malignant melanoma. There is necrosis of the overlying epidermis, and the pleomorphic tumour cells have large, hyperchromatic nuclei. (Haematoxylin and eosin, ×400).*

9·4 yr, with all of the surviving cases being followed up for 5 yr or more. Of the 12 patients four died, with evidence of metastasis in three of them. The remaining death occurred a few hours after surgery for removal of a local recurrence. One of the patients who died underwent a block dissection of the neck for cervical lymph node metastasis one year after the initial excision, death from multiple metastasis occurring some 10 yr later. In one surviving patient (No. 21) the initial removal was incomplete, and a second surgical excision was required six months afterwards: she is alive and well four years after the first operation.

Unclassified malignant melanoma. The three patients in this group were followed up for 12, seven, and eight years respectively. The single fatality

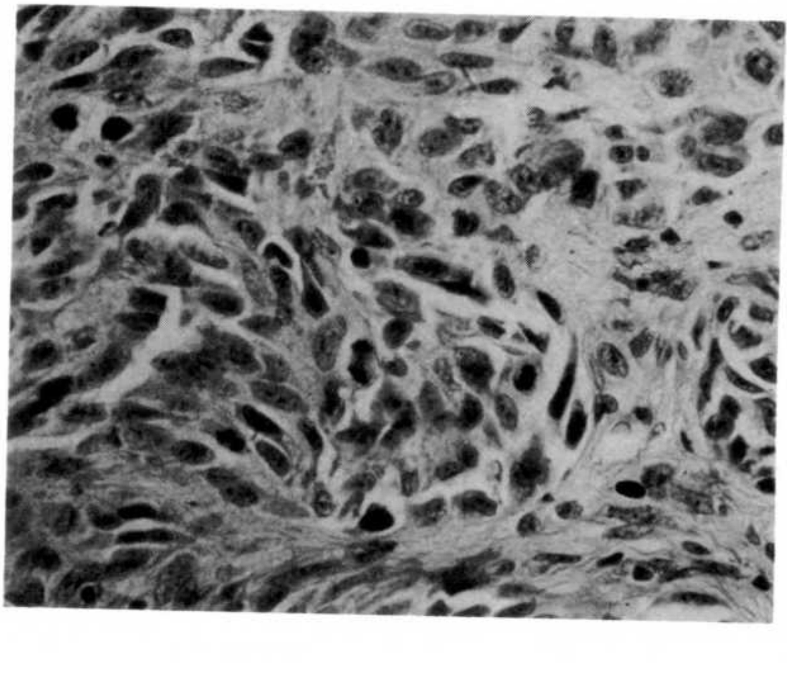

Fig. 10 *Case 19. Nodular malignant melanoma. Many of the cells are spindle-shaped and mitotic activity is evident. (Haematoxylin and eosin, ×400).*

Table 1 *Histopathological details and response to treatment in malignant melanoma of the eyelid skin*

Case no.	*Age*	*Sex*	*Type*	*Histology*					*Initial therapy*	*Recur. (yr)*	*Follow-up (yr)*	*Comments*
				Thickness (mm)	*Melanin*	*Mitoses*	*Pleomorphism atypia*	*Nucleolus*				
1	52	F	Superficial Spreading	0·4	+	–	+	+	Excision	–	Alive 3	
2	58	F		0·1	+	–	+	±	"	–	Alive 4	In situ
3	62	F	"	0·5	+	–	±	±	Irradiation		Dead 7	Dead with metastases
4	61	M	"	–	±	–	+	±	"		Dead 12	Thickness not measurable
5	69	F	"	2·2	–	±	±	±	Excision	–	Alive 10	
6	62	M	"	0·5	+	–	±	±	"	–	Alive 3	
7	37	F	"	0·2	+	±	+	+	"	–	Alive 10	In situ with early invasion
8	65	F	"	0·3	+	±	+	+	"	–	Alive 4	
9	40	M	"	0·2	+	–	±	±	"	–	Alive 14	
10	55	M	Nodular	3·3	–	+	+	±	"	–	Dead 2	Metastases after after 1½ yrs
11	65	F	"	3·2	±	+	+	+	"	½	Alive 7	Initial removal incomplete
12	39	M	"	2·9	–	+	+	±	"	–	Alive 17	
13	50	F	"	>2·5	±	+	+	±	"	–	Alive 7	
14	24	F	"	1·4	–	–	+	±	"	–	Alive 14	
15	35	M	"	1·7	±	–	±	±	"	–	Dead 5	Lymphnode and cerebral metastases
16	57	M	"	2·5	–	±	±	+	"	–	Dead 11	Block dissection 1971 (cervical node metastasis, died 1981)
17	43	F	"	1·2	+	–	+	±	"	–	Alive 33	Evidence of preceding naevus
18	43	F	"	1·5	–	±	±	+	"	–	Alive 6	
19	18	F	"	3·9	±	±	+	±	"	–	Alive 6	
20	64	M	"	1·4	±	+	+	–	"	1	Dead 1	Died post-op. (recurrence)
21	68	M	"	3·0	+	±	+	+	"	½	Alive 4	Initial removal incomplete
22	80	F	Unclassifiable	–	–	+	+	+	Excision/ irradiation		Dead 12	Died natural causes
23	69	F	"	<5·5	+	+	+	+	Excision	–	Alive 7	
24	74	F	"	–	–	±	±	±	"	–	Alive 8	

concerned the first of them (No. 22), an 80-year-old female who died of natural causes at the age of 92 years. Findings in individual cases are given in Table 1.

Discussion

Dermatopathologists commonly distinguish three types of cutaneous malignant melanoma. In our series we identified the nodular and superficial spreading forms but not the melanoma arising from a Hutchinson's freckle (lentigo maligna). This is unlikely to be a significant omission, however, others having described both the preinvasive[6] and invasive form[7] of the latter variant in the eyelids.

Superficial spreading malignant melanoma was diagnosed in nine patients (37·5% of the total), which is below the 70% incidence cited for the skin in other sites.[8] In two of these cases the proliferation was largely intraepithelial, with minor evidence of deep invasion. Although the intraepidermal component was pigmented in all but one case, the melanin content of the stromal component was usually less evident, while the cells in this region were often spindle-shaped. The overall survival in this group, i.e., two tumour-related deaths in nine patients followed up for three to 14 years, is comparable to the 31% mortality after 5 years pertaining to this type of melanoma in general.[9]

Nodular malignant melanoma was the most frequent variant in our series (50% of the total), which is considerably in excess of the 12% cited for skin melanoma as a whole.[9 10] In four patients the tumour appeared to have originated at the lid margin and proliferated to create a fairly discrete compact nodule, with variable cytological pleomorphism and a dearth of pigment: two of these cases died as a result of metastasis and one who is alive and well needed further treatment for a local recurrence. The fourth also suffered a local recurrence and died a few hours after surgery on this account. The prognosis for tumours of the nodular variety in other situations is generally worse than for other types of cutaneous melanoma, an overall five-year survival of 44% having been quoted.[9] Consequently the 25% mortality (16·7% after five years) for the 12 patients with this type of melanoma in the eyelid, seven of whom have survived more than five years, compares favourably with nodular malignant melanoma presenting at other sites. Early diagnosis and treatment prompted by the conspicuous location of the tumour may be a factor in the relatively better prognosis. But it is possibly patients with a nodular lesion developing at the mucocutaneous lid margin who are at greatest risk, since two of four such cases have had a fatal outcome and a third developed a local recurrence, whereas only one of eight patients in whom the tumour was confined to the skin has died. The cause of this unexpected finding is obscure, but specific aspects of eyelid anatomy may be involved, particularly the presence of efferent blood and lymph vessels at the margin, together with repeated minor trauma occasioned by blinking.

The prognosis of cutaneous malignant melanoma relates also to the depths of invasion.[8 11 12] A similar consideration applies to malignant melanoma of the conjunctiva, where a thickness of under 1·5 mm usually implies a favourable outcome after treatment.[13 14] The maximum tumour thicknesses in the four patients with a fatal outcome in whom it was possible to take measurements were 0·5, 3·3, 1·7, 2·5 mm respectively. There were, however, eight patients in whom the tumour measured 1·5 mm or more who were alive and well at the time of review. To some extent the curvature of the eyelid at the margin where it meets the conjunctiva makes it difficult to determine the point from which measurements of thickness should be made, but even with this allowance the impression gained is that, size for size, malignant melanoma of the eyelid skin has a slightly better prognosis than its counterpart elsewhere. Whether a grading based on the tissue level reached by the invading tumour is applicable to the eyelid is debatable, since the total dermis (both papillary and reticular) is exceptionally thin in this region, and a stage V melanoma on the Clark *et al.*[10] scale would often be a much smaller lesion than such staging would represent in other parts of the integument. For this reason we have chosen to confine ourselves to simple thickness measurements.

The generally good response to surgical excision suggests that this is the preferred treatment. Of the 21 patients with surgery three had a tumour related death, but both the patients treated with irradiation died with metastases. In none of the patients treated with primary surgery was there evidence of local recurrence. Only two patients developed cervical lymphnode metastases, one of them undergoing a cervical block dissection, but the other had cerebral metastasis diagnosed at the same time.

Finally we consider that the possible late presentation of metastases means that this and any similar study must follow up patients for at least 15 years.

The authors thank Miss G Chrysanthopoulou, Miss R Hart, Mrs P Goodwin, Dr J M Henk, P v Heerde, and Miss J A M Haages for their co-operation and aid in this study. We also thank the several unnamed surgeons for their unequivocal and prompt return of the questionnaires.

References

1 Henkind P, Friedman A. Cancer of the lids and ocular adnexa. In: Andrade R, Gumport SL, Popkin GL. *Cancer of the skin: biology, diagnosis, management.* Philadelphia: Saunders, 1976; **13:** 45–71.
2 Batsakis J. *Tumors of the head and neck.* Baltimore: Williams and Wilkins, 1974.
3 Levene A. On the histological diagnosis and prognosis of malignant melanoma. *J Clin Pathol* 1980; **33:** 101–24.
4 McGovern VJ, Mihm MC, Bailly C, *et al.* The classification of malignant melanoma and its histologic reporting. *Cancer* 1973; **32:** 1446–57.
5 Kopf AW, Bart RS, Rodriguez-Sains RS. Malignant melanoma: a review. *J Dermatol Surg Oncol* 1977; **3:** 41–125.
6 Rodriguez-Sains RS, Jakobiec FA, Iwamoto T. Lentigo maligna of the lateral canthal skin. *Ophthalmology* 1981; **88:** 1186–92.
7 Naidoff MA, Bernardino VB, Clark WH. Melanocytic lesions of the eyelid skin. *Am J Ophthalmol* 1981; **82:** 371–82.
8 Clark WA Jr, Ainsworth AM, Bernardino EA, *et al.* The developmental biology of primary human malignant melanomas. *Semin Oncol* 1975; **2:** 83–103.
9 Kopf AW, Bart RS, Rodriguez-Sains RS, Ackerman AB. *Malignant melanoma.* New York: Masson, 1979.
10 Clark WH, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behaviour of primary human malignant melanomas of the skin. *Cancer Res* 1969; **29:** 705–26.
11 Breslow A. Tumor thickness, level of invasion and node dissection in stage 1 cutaneous melanoma. *Ann Surg* 1975; **182:** 572–5.
12 McGovern VJ. The classification of melanoma and its relationship with prognosis. *Pathology* 1970; **2:** 85–98.
13 Silvers DN, Jakobiec FA, Freeman TR, Lefkowitch JH, Elie RC. Melanoma of the conjunctiva: a clinicopathologic study. In: Jakobiec FA, ed. *Ocular and adnexal tumors.* Birmingham, Ala: Aesculapius, 1978: 583–99.
14 Liesegang TJ, Campbell RJ. Mayo Clinic experience with conjunctival melanomas. *Arch Ophthalmol* 1980; **98:** 1385–9.

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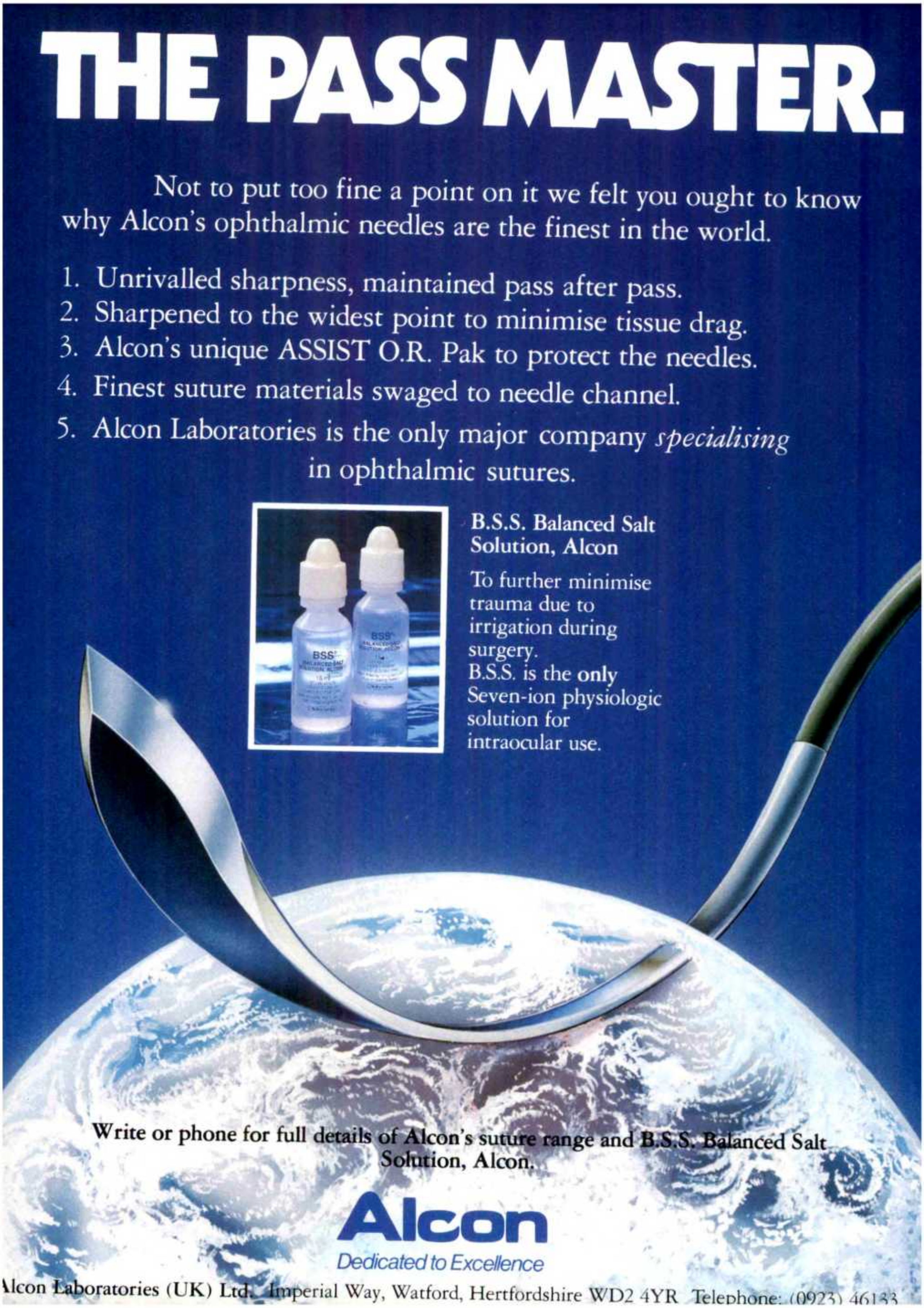

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British Journal of Ophthalmology, 1985, **69**, 187–188

Capnocytophaga keratitis

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SUMMARY We report two cases of bacterial keratitis caused by *Capnocytophaga*, a genus of capnophilic Gram negative bacilli. Both responded to topical and subconjunctival clindamycin.

Capnocytophaga is a genus of gliding Gram negative bacilli that is part of the normal gingival flora. This organism may also be an opportunistic pathogen and has been isolated from blood, transtracheal aspirate, and spinal fluid[1]. We describe the first two cases of bacterial keratitis caused by this organism and provide treatment recommendations.

Case reports

CASE 1

A 43-year-old woman with neovascular glaucoma and corneal oedema developed a 15 mm² suppurative corneal ulceration with adherent endothelial plaque and hypopyon. Despite hourly topical 5% and daily subconjunctival 100 mg cefazolin no improvement occurred during the first 72 hours. Initial corneal scrapings subsequently showed moderate growth of *Capnocytophaga ochracea* on blood and chocolate agar plates. Because broth dilution sensitivity testing showed a minimal inhibitory concentration (MIC) less than 0·125 µg/ml (mg/l) for clindamycin, cefazolin was discontinued, and clindamycin was instituted topically (5%, one drop every 15 minutes) and subconjunctivally (75 mg, twice daily). Progressive improvement occurred with re-epithelialisation and reduced stromal inflammation. Topical prednisolone acetate 1% was later added, and the medications were then gradually tapered. Visual acuity was limited by proliferative diabetic retinopathy.

CASE 2

Four days after blunt ocular trauma a 35-year-old black man developed a 5·9 mm² suppurative corneal ulcer involving the anterior two thirds of the corneal stroma with an inflammatory plaque. Gram stained smears of corneal scrapings showed numerous polymorphonuclear leucocytes but no micro-organisms. Topical 1·4% gentamicin and 5% cefazolin were begun in addition to twice daily subconjunctival injections of 20 mg gentamicin and 100 mg cefazolin. During the next three days stromal suppuration increased, a circumferential limbal infiltrate appeared, and progressive thinning occurred. Moderate growth of *Capnocytophaga sputigena* was identified on blood and chocolate agar culture plates sensitive to clindamycin with an MIC of 0·25 µg/ml (mg/l). Antibacterial medications were changed to topical (5%, one drop every 15 min) and subconjunctival (75 mg, twice daily) clindamycin. Twenty four hours after treatment with clindamycin the disease had stopped progressing and after 48 hours substantial improvement had occurred with decreased corneal oedema. The cornea continued to clear after administration of topical 1% prednisolone acetate.

Discussion

Capnocytophaga are unique Gram negative bacilli that have gliding motility and capnophilic metabolism with production of acetate and succinate.[1 2] Using morphological and chemotaxonomic data we found the genus to be distinct from bacteroides, and it can be separated into three species: *C ochracea*, *C sputigena*, and *C gingivalis*. These organisms are part of the normal oral microflora and are occasionally responsible for periodontitis. Other infections such as septicaemia,[3] endocarditis,[4] and cervical abscess[5] have also occurred, especially in immunocompromised patients.

Bacterial keratitis has not previously been described as being due to capnocytophaga. While we did not identify the organism on the initial Gram stained smears, cultures of corneal scrapings subsequently showed a moderate growth on multiple

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solid media. There was no distinguishing clinical feature, but both patients presented with suppurative keratitis in a previously diseased or traumatised cornea. Future improvements in microbiological evaluations, such as biochemical assays of capnine[6] or immunological testing,[7] may prove useful in the diagnosis of these infections.

In-vitro sensitivity testing of capnocytophaga strains has shown susceptibility to penicillin G, cephalosporins, clindamycin, chloramphenicol, and tetracycline but relative resistance to aminoglycosides, polymyxins, and vancomycin.[8] Since the in-vitro testing and clinical course of both cases of suppurative keratitis reported here showed improvement after therapy with local clindamycin, and because topical clindamycin has shown adequate corneal penetration in the experimental animal,[9] this antibiotic can be considered when anaerobic Gram negative bacilli are isolated from a corneal ulcer unresponsive to other antibacterial agents.

These two cases of corneal ulcers caused by an unusual micro-organism show the need to do corneal scrapings for microbiological evaluation whenever bacterial keratitis is suspected. Laboratory sensitivity testing is useful to guide the selection of alternative antimicrobial agents.

Microbiological testing was done by Nettie M Robinson of the Ocular Microbiology Laboratory, Baylor College of Medicine, Houston, Texas; and Vera Sutter from the Wadsworth Veterans Administration Hospital, Los Angeles, California.

References

1 Newman MG, Sutter VL, Pickett MJ, *et al.* Detection, identification, and comparison of *Capnocytophaga*, *Bacteroides ochraceus*, and DF-1. *J Clin Microbiol* 1979; **10:** 557–62.
2 Collins MD, Shah HN, McKee AS, Kroppenstedt RM. Chemotaxonomy of the genus *Capnocytophaga* (Leadbetter, Holt and Socransky). *J Appl Bacteriol* 1982; **52:** 409–15.
3 Gandola C, Butler T, Badger S, Cheng E, Beard S. Septicemia caused by capnocytophaga in a granulocytopenic patient with glossitis. *Arch Intern Med* 1980; **140:** 851–2.
4 Coignard S, Malbrunot C, Bor Y, *et al.* Endocardite á *Capnocytophaga ochracea. Nouv Presse Med* 1982; **11:** 1338.
5 Seger R, Kloeti J, von Graevenitz A, *et al.* Cervical abscess due to *Capnocytophaga ochracea. Pediatr Infect Dis* 1982; **1:** 170–2.
6 Godchaux W III, Leadbetter ER. Unusual sulfonolipids are characteristic of the *Cytophaga-Flexibacter* group. *J Bacteriol* 1983; **153:** 1238–46.
7 Murayama Y, Mashimo PA, Tabak LA, Levine MJ, Ellison SA. Isolation and partial characterization of a genus common antigen and species specific antigen of capnocytophaga. *Jpn J Med Sci Biol* 1982; **35:** 153–70.
8 Sutter VL, Pyeatt D, Kwok YY. In vitro susceptibility of capnocytophaga strains to 18 antimicrobial agents. *Antimicrob Agents Chemother* 1981; **20:** 270–1.
9 Mercer KB, DeOlden JE, Leopold IH. Intraocular penetration of topical clindamycin in rabbits. *Arch Ophthalmol* 1978; **96:** 880–4.

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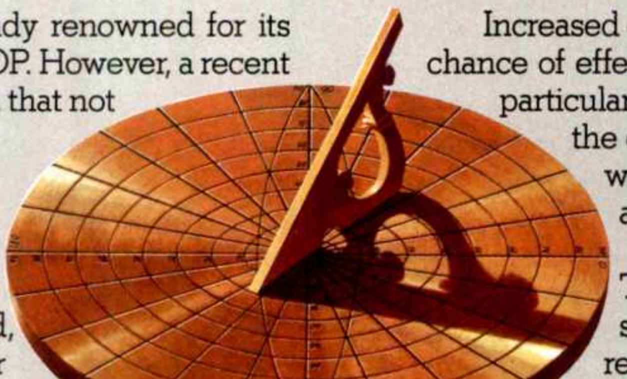

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REFERENCES
1. Sponsel, W. E., *et al.*, *Brit. J. Ophthal.*, 1983, 67, 220.
2. Norell, S. E., *Amer. J. Ophthal.*, 1981, 92, 727.
3. MacKean, J. M., and Elkington, A. R., *Brit. J. Ophthal.*, 1983, 67, 46.
4. Reynolds, P. M., *Glaucoma*, 1982, 262.
5. Willcockson, J., and Willcockson, T., *Glaucoma*, 1982, 155.

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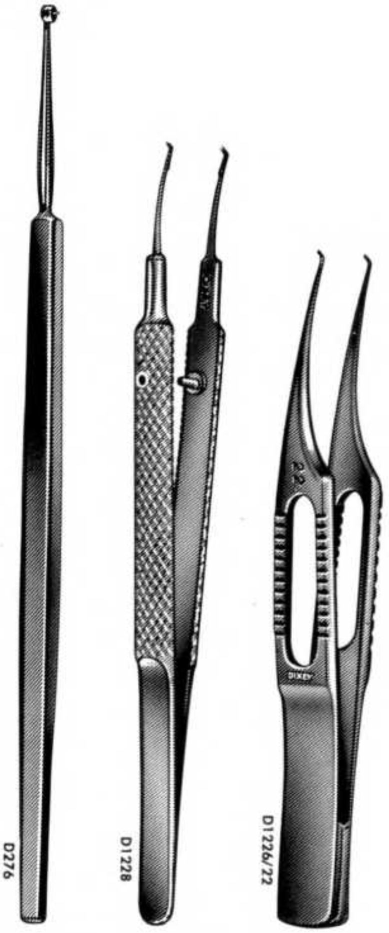

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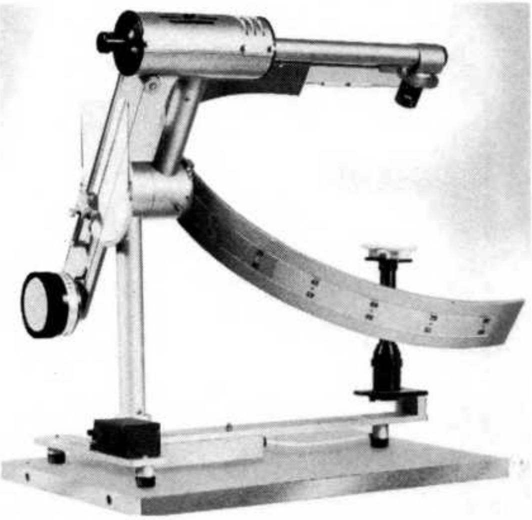

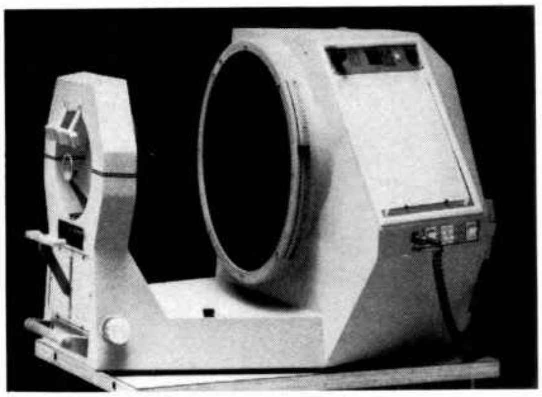

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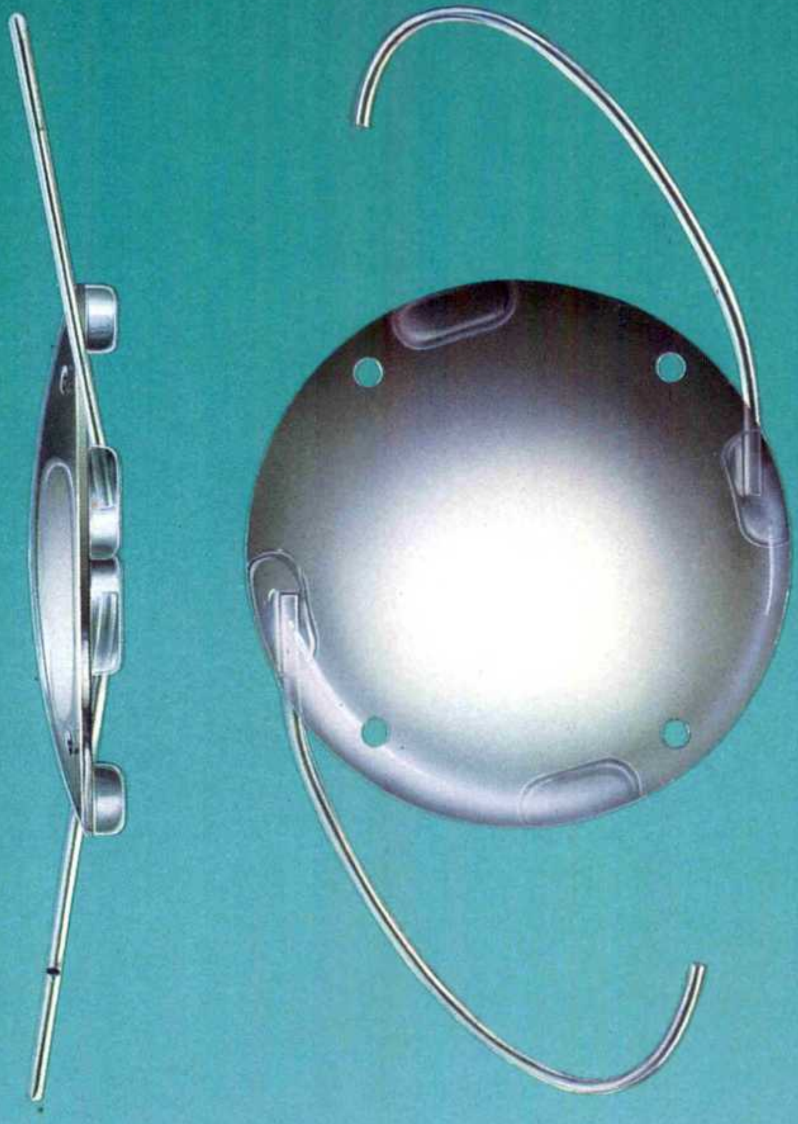

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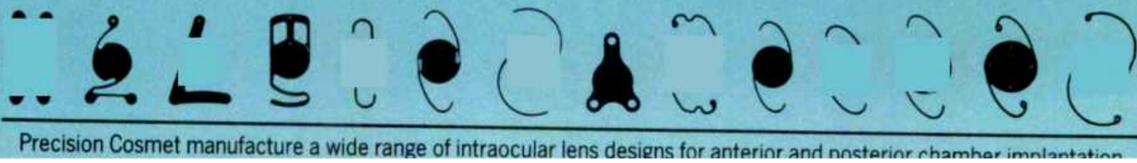

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British Journal of Ophthalmology, 1985, **69**, 189–191

Gentamicin-resistant Pseudomonas endophthalmitis after penetrating keratoplasty*

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SUMMARY A case of pseudomonas endophthalmitis after penetrating keratoplasty is described. Bacterial sensitivities in this case and in five of six previously reported cases of endophthalmitis after corneal transplant showed resistance to gentamicin, an antibiotic routinely used in the transport medium. The recovery of antibiotic resistant bacteria in antibiotic supplemented media is discussed with emphasis on prevention.

Bacterial endophthalmitis is an uncommon but potentially devastating complication of penetrating keratoplasty. A major source of this kind of infection in corneal transplantation can be the donor material or contaminated medium. We describe a case of pseudomonas endophthalmitis complicating McCarey-Kaufman (M-K) media, its management, and methods for further prevention.

Case history

On 26 March 1981 a 74-year-old woman had an 8·5 mm/8·0 mm penetrating keratoplasty with vitrectomy of the left eye for aphakic bullous keratopathy. On the first postoperative day a small central epithelial defect was noted. The anterior chamber was deep, and a small fibrin clot was present. On the second postoperative day a culture was taken and the donor rim was found to have a Gram negative bacillus. Treatment consisting of topical gentamicin and Decadron (dexamethasone) was maintained. Examination early on 29 March 1981, the third postoperative day, showed a hypopyon at the inferior graft interface. The eye was more injected, and the anterior chamber reaction was also more intense. Endophthalmitis was suspected and, because of initial antibiotic sensitivities of the donor rim, the patient was started on ticarcillin 3 g intravenously every four hours and a pars plana vitrectomy was done. Vitreous cultures were obtained and intravitreal injections of carbenicillin, cephradine, and amikacin were given. Postoperatively the patient was started on prednisone 20 mg orally qid and carbencillin 3 g intravenously four-hourly. Atropine 1%, Decadron, and fortified gentamicin drops (14 mg/ml) were all given topically in the left eye. On 30 March 1981 after the vitrectomy there was a marked cellular reaction and a 50% hypopyon (Fig. 1). Examination on 2 April 1981 showed that the hypopyon had begun to clear. On 7 April 1981 all intravenous antibiotics were stopped, and the patient was discharged on 10 April 1981. Visual acuity on 7 December 1981 was 20/300 with a clear graft.

The donor rim was completed on 31 March 1981 and grew a pure culture of *Pseudomonas aeruginosa*

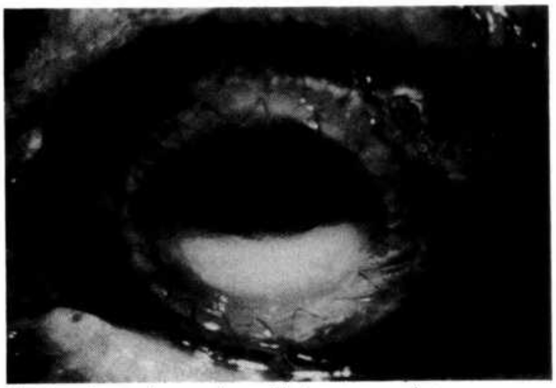

Fig. 1 *Corneal transplant with hypopyon after vitrectomy.*

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*Presented in part at the Southeast Regional Eye Bank Meeting, New Orleans, Louisiana, in June 1982.

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sensitive to carbenicillin, sulphonamide, and amikacin and resistant to ampicillin, chloramphenicol, gentamicin, and cephalothin. Serological typing showed the organism isolated from the donor rim to be identical to the vitreous isolate. A minimum inhibitory concentration (MIC) test was done on the organism to gentamicin, which was greater than 160 µg/ml. A gentamicin assay was obtained from the original corneal transport M-K fluid, which showed a concentration of 49 µg/ml (mg/l).

Discussion

LeFrançois and Baum[1] reported on the first encounter with bacterial endophthalmitis after keratoplasty. The donor cornea was irrigated with Neosporin (neomycin, gramicidin, polymyxin B) drops prior to removing the rim, and gentamicin was added to the M-K culture medium to make a final concentration of 6 µg/ml. Cultures of the residual donor cornea, the culture media, and from the anterior chamber all grew a 'pseudomonas species' resistant to gentamicin and carbenicillin. The corneal graft eventually developed severe stromal oedema, and the globe slowly became phthisical. The authors believe the following factors may combine to produce a greater incidence of endophthalmitis by a more resistant pathogen with the use of M-K storage. (1) a larger potential inoculum due to (*a*) increased length of storage, (*b*) the possibility that tissue culture fluid encourages growth of micro-organisms; (2) contamination of the endothelial surface of the donor cornea; (3) the emergence of more antibiotic resistant micro-organisms in antibiotic supplemented media.

Reports by Shaw,[2] Khodadoust,[3] and Escapini[4] have further substantiated that contamination of donor material can lead to bacterial infection in the host. Cultures obtained from these three cases grew *Streptococcus pneumoniae* with no antibiotic sensitivites reported; *Pseudomonas aerugenosa* sensitive only to carbenicillin; and *Staphylococcus aureus* resistant to chloramphenicol, clindamycin, streptomycin, gentamicin, and penicillin.

More recently Leveille *et al.*[5] described four cases of endophthalmitis (three with positive donor rims) in 1876 penetrating keratoplasties. M-K media with gentamicin added at the eye bank was used in all instances. Cultures of the organisms taken from the patient and donor rims showed: case 2, *Pseudomonas aeruginosa*, resistant to gentamicin and the subject of this report; case 3, group D streptococcus sensitive to gentamicin; and case 4, *Streptococcus pneumoniae* without antibiotic sensitivities.

Recommendations for the use of M-K medium to improve corneal preservation prior to penetrating keratoplasty includes cold storage between 4° to 8°C and the addition of gentamicin 100 µg/ml to inhibit bacterial growth. Any effort, however, to sterilise donor corneas in transport medium with fortified antibiotics cannot be relied upon with impunity. In fact various clinical case reports, including ours, suggest that antibiotic supplemented M-K medium does not sterilise the medium prior to keratoplasty in all instances.

Several authors, indeed, have evaluated the effects of time and temperature on bacterial recovery in M-K medium supplemented with antibiotics.[6 7] The results of these studies cast doubt against the expectation that M-K medium with antibiotic, as usually used, will reliably kill even sensitive bacteria.

The recovery of gentamicin resistant bacteria (in our case MIC greater than 160 µg/ml and in five of six cases that developed endophthalmitis where antibiotic sensitivities were reported) in gentamicin-supplemented media poses a new problem in the prevention of postoperative infection. No matter what precautions are taken, or what kinds or doses of antibiotic are used prophylactically, some contamination resistant to all these measures is possible. Because of the isolation of gentamicin-resistant organisms we believe storage medium containing gentamicin should be refrigerated at 4°C to inhibit the growth of gentamicin-resistant organism. It should then be allowed to reach room temperature one to two hours before corneal transplantation in order for the gentamicin to exert its effect upon gentamicin-sensitive bacteria.

To help further reduce the risk of donor to host transmission of disease we recommend that patients undergoing cornea transplant surgery be treated with parenteral broad spectrum antibiotics, in addition to topical therapy with gentamicin (to cover gentamicin-sensitive organisms) until the results of the culture and sensitivities of the donor rim are complete. It has been the policy of one of us (MSI) to give intravenous cephaloridine or piperacillin prophylactically at the time of surgery and to continue such therapy for at least 72 hours postoperatively.

We further emphasise that, although it is not practicable to culture donor corneas once they are immersed in antibiotic supplemented M-K medium, and post-mortem culture results are misleading, it is mandatory to culture the donor rim at the time of surgery.

Finally, an awareness that infection can be transmitted from the donor cornea may also help prevent its occurrence.

References

1 Le François M, Baum JL. Flavobacterium endophthalmitis following keratoplasty. Use of a tissue culture medium-stored cornea. *Arch Ophthalmol* 1976; **941:** 907–1909.

2 Shaw EL, Aquavella JV. Pneumococcal endophthalmitis following grafting of corneal tissue from a (cadaver) kidney donor. *Ann Ophthalmol* 1977; **9:** 435–40.

3 Khodadoust AA, Franklin RM. Transfer of bacterial infection by donor cornea in penetrating keratoplasty. *Am J Ophthalmol* 1979; **87:** 130–2.

4 Escapini H, Olson RJ, Kaufman HE. Donor cornea contamination with McCarey-Kaufman medium preservation. *Am J Ophthalmol* 1979; **88:** 59–62.

5 Leveille AS, McMullan FD, Cavanagh HD. Endophthalmitis following penetrating keratoplasty. *Ophthalmology* 1983; **90:** 38–9.

6 Baum J, Barza M, Kane A. Efficacy of penicillin G, cefazolin, and gentamicin in M-K medium at 4°C. *Arch Ophthalmol* 1978; **96:** 1262–4.

7 Graul EE Jr, Olson RJ, Janney A. Resistance of *Pseudomonas aeruginosa* to modern eye-banking technique. *Ann Ophthalmol* 1980; **12:** 429–32.

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Granulomatous uveitis in neurological disease

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SUMMARY Five women with granulomatous uveitis were diagnosed as having probable multiple sclerosis. Three of the women developed curious iris nodules that resolved with topical prednisolone acetate treatment. The association of granulomatous type uveitis, with or without iris nodules, should alert the ophthalmologist to inquire about neurological symptoms attributable to multiple sclerosis.

The association of multiple sclerosis and granulomatous uveitis was first observed by Wuseke.[1] However, more commonly pars planitis and/or periphlebitis retinae has been emphasised as a common finding in patients with multiple sclerosis.[2-18] It is the purpose of this paper to report five patients with probable multiple sclerosis who developed a pars planitis-like picture in addition to curious iris nodules and granulomatous uveitis.

Case reports

CASE 1

A 39-year-old Caucasian woman developed decreased sensation on the right side of her face, transient diplopia, slurred speech, and clumsiness. The cerebrospinal fluid protein was 36 mg/dl (0·36 g/l) with a gammaglobulin concentration of 12·4 mg/dl, =0·124 g/l (normal 8·8, SD 2·6 mg/l, =0·09± 0·03 g/l), and 4 white blood cells/mm^3. A tuberculin skin test and a test for HLA-B27 were negative. Serum calcium was 9·1 mg/dl, =2·3 mmol/l (normal 8·7–10·2 mg/l, =2·2–2·5 mmol/l); serum B_{12} was 440 (normal 200–1000) pg/ml (ng/l). A pattern-reversal visual evoked potential showed normal latencies of 119 in the right eye, and 166 ms in the left eye. A brain computerised tomographic scan showed two definite periventricular areas of contrast enhancement on the left side of the cerebral cortex and two more similar questionable areas of contrast enhancement in the left temporal lobe and right occipital horn. These were thought to be most consistent with demyelinating disease. The patient was diagnosed as having multiple sclerosis.

She stated she had noted floaters for five years, and her referring ophthalmologist had treated her for recurrent iritis. Examination of the eyes showed her vision to be 20/40 (6/12) right eye and 20/40 (6/12) left eye. Eye movements were full without evidence of internuclear ophthalmoplegia. Both eyes had 1+ anterior chamber cell and flare and 2+ fine cells in the anterior vitreous. The right macula was oedematous. Both eyes had patchy retinal venous sheathing and inferior vitreous fluffball opacities. There was slight temporal optic nerve pallor, but Goldmann fields were full. Six months later she developed large, lardaceous keratic precipitates and grey-brown, round nodules at the pupillary border of the left eye (Fig. 1). The nodules disappeared on treatment with topical prednisolone acetate 1%, only to recur on cessation of topical steroids.

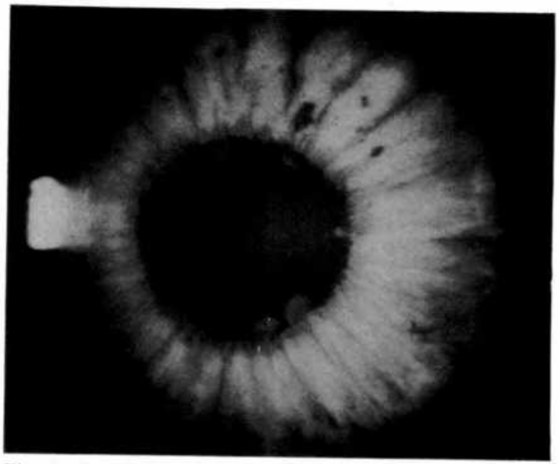

Fig. 1 *Iris nodules at pupillary margin in patient with probable multiple sclerosis.*

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CASE 2

A 50-year-old Caucasian woman presented with recurrent iritis. Her neurological problems began at age 18, when she had developed severe right sided headaches, exacerbated by combing her hair, and transient numbness of the right hand and arm. At age 28 she awoke one day with pain and blurred vision in the right eye and diplopia on left gaze. She was not examined by an ophthalmologist, but a neurologist found a left central scotoma and inferotemporal scotoma. There was also mild weakness of the right hand and arm and a decrease in stereognosis. No cerebrospinal fluid protein electrophoresis was done in 1953. A tuberculin skin test was negative. Chest *x*-ray and pneumoencephalography were normal. A carotid arteriogram was interpreted as showing spasm of cerebral arteries. After the arteriogram she suffered a right hemiparesis and aphasia that resolved over 48 hours, leaving a residual right hemisensory deficit. She was diagnosed as having either multiple sclerosis or an unusual cerebral vasculitis. At age 31 she developed paraesthesias of the left lower extremity and binaural hearing loss. At age 41 she had a hernia of the intervertebral disc between L4 and L5 and underwent laminectomy. At age 48 a right ptosis was noted. Her gait became somewhat broad-based over the next two years.

At age 50 she was referred for ophthalmological examination. Her best corrected visual acuity was RE 20/40-2 (6/12) and LE 20/25 (6/7·5). There was 2+ ciliary flush, large lardaceous keratic precipitates, and 1+ anterior chamber cells in both eyes. There was a posterior synaechia in the right eye. The iris of the left eye had a raised brown nodule on the surface of the stroma at 7 00 o'clock. Numerous fluffballs were present in the inferior vitreous of both eyes, but no snowbanking was seen on the pars plana. An HLA-B27 test was positive. However, a rheumatologist thought she probably did not have ankylosing spondylitis. A VDRL was negative. The erythrocyte sedimentation rate was 12 mm/h and serum calcium was 8·9 mg/dl (2·2 mmol/l). Her iritis resolved, and the iris nodule disappeared on topical prednisolone drops. Pseudoexfoliation of the left lens capsule was noted one year later. Six years later she developed sheathing of peripheral retinal venules and bilateral macular oedema.

At age 57 a neurological examination showed proximal leg weakness, normal upper extremity strength, but mild adiadochokinesia of both hands. Deep tendon reflexes were diffusely brisk with bilateral unsustained ankle clonus. There was decreased awareness to pin prick in the right arm and leg, decreased vibration sense in the right ankle, and decreased position sense in all toes. No dysmetria of the arms was present, but this was not tested in the legs because of the leg weakness. Serum angiotensin converting enzyme was normal at 19 (normal 10–30) units/ml. Her neurologist thought the most likely diagnosis was multiple sclerosis. Other possibilities included an obscure, chronic meningoencephalitis such as Harada's disease, or sarcoidosis, though the latter was very unlikely in view of the normal chest *x*-ray, serum calcium, and normal angiotensin converting enzyme level.

CASE 3

A 38-year-old Caucasian woman developed a severe headache. One week later she awoke with an uncomfortable pressure sensation in the left orbital area. Later that same day she observed a horizontal black line with a bright line at one end in her left visual field. Over several hours the vision in the left eye became totally grey. An ophthalmological examination several days later showed vision in the right eye to be 20/40 (6/12). With the left eye she could only count fingers at 1 foot (30 cm). There was a left relative afferent pupillary defect. Eye movements were normal. The optic nerve and retina were normal in both eyes. The diagnosis of left retrobulbar neuritis was made, and she was treated with prednisone 60 mg orally for five days. The vision in the left eye gradually improved but did not return to its previous level.

In the ensuing months she noticed difficulty in coordinating her hands, trouble with her balance and gait, and decreased hearing in the left ear. The past medical history showed emotional problems and heavy drinking, for which she had received psychiatric care. Further, she had suffered a closed head injury with loss of consciousness two years previously. Her sister had been diagnosed as having definite multiple sclerosis.

Examination of the eyes six months after the initial episode of decreased vision in the left eye showed best corrected visual acuity of RE 20/20 (6/6) and LE 20/100 (6/30). There was a mild left relative afferent pupillary defect. On colour vision testing in the right eye she missed plates one and four of the HRR (Hardy, Rand, Rittler) pseudoisochromatic plates but arranged the Farnsworth D-15 and Nagel anomaloscope correctly. With the left eye she failed all these tests. The visual field in the right eye was normal. In the left visual field a small central scotoma to the I-4e test object was present. Eye movement testing showed non-smooth pursuit to the patient's left, decreased optokinetic nystagmus with the drum rotating to the patient's left, and poor suppression of the vestibulo-ocular reflex on rotation to her left. Several moderate-sized lardaceous keratic precipitates were present on the corneal endothelium of both eyes. There was an occasional cell in the

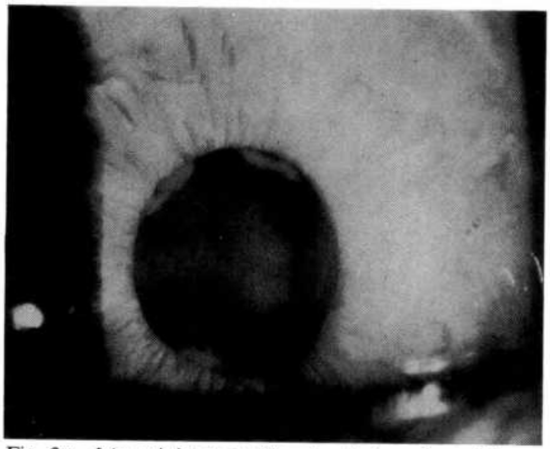

Fig. 2a *Iris nodules at pupillary border in patient with multiple sclerosis.*

anterior chamber in both eyes. Numerous large nodules were present at the pupillary border of the left eye (Fig. 2a). There were many fine, white cells in the anterior vitreous of both eyes. The disc in the right eye was normal. The left disc was pale. There were irregularities of the calibre of peripheral retinal arterioles in the left eye. The iris nodules resolved on topical prednisolone acetate drops.

A neurological examination showed mild left-sided limb dysmetria and bilaterally hypotonic deep tendon reflexes. Laboratory examination showed a cerebrospinal fluid protein of 0·69 g/l, 60 white blood cells/mm^3 with 83% lymphocytes, and a cerebrospinal fluid gammaglobulin of 10·2 mg/l (0·1 g/l) (normal 0–0·035 g/l). A chest *x*-ray was normal. No consistent responses were found with monocular stimulation on visual evoked potential testing. Varying major peaks were present with both eyes stimulated. Auditory evoked and somatosensory potentials were normal. Serum and cerebrospinal fluid VDRL were non-reactive. An electroencephalogram was normal. Computerised tomography of the brain and orbits was normal. Serum protein immunoelectrophoresis showed a raised IgM of 400 (normal 36–266) mg/dl (4 (normal 0·36–2·7 g/l) and normal levels of IgG and IgA. Antinuclear antibodies were less than 1:20 dilution, which is normal. A lupus erythematosus cell preparation was negative. Purified protein derivative (PPD) testing was negative at 48 hours, but tests for trichophyton and mumps were positive. Serum angiotension converting enzyme level was 28 (normal 10–30) units/ml. The white blood cell count was slightly raised at $10{\cdot}5\times10^9$/l, with 5% eosinophils. The patient had HLA-B7 but not HLA-B27. This patient was thought to have multiple sclerosis because of a left retrobulbar neuritis, a left visual pursuit deficit (signifying a left parietal lobe lesion), and a raised cerebrospinal fluid gammaglobulin.

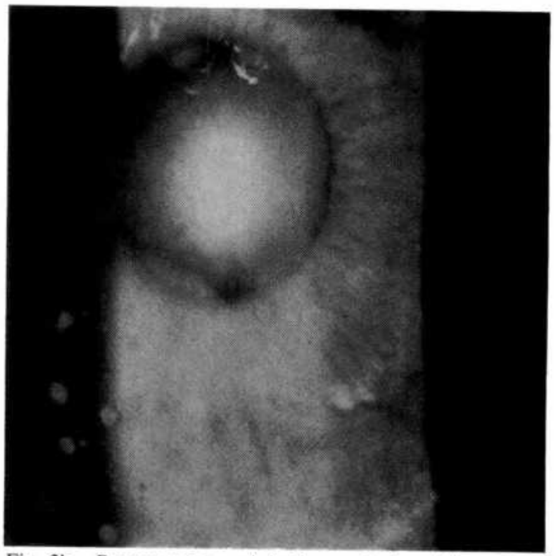

Fig. 2b *Recurrent iris nodules in association with lardaceous keratitic precipitates in same patient.*

The patient did well on medication until one year later, when she noted decreased vision and a vibrating sensation of the left eye. There was a fibrinous iritis of the left eye with several posterior synechiae and several pupillary iris nodules. Fine vitreous cells and large fluffballs were noted in the inferior vitreous of both eyes. In addition the right eye showed large iris pupillary nodules and lardaceous keratic precipitates (Fig. 2b). Topical prednisolone acetate therapy was started and the iris nodules disappeared. Intravenous fluorescein angiography was normal at that time but eight months later showed bilateral cystoid macular oedema.

CASE 4

A 52-year-old black West Indian nun presented with decreased vision in the left eye. Best corrected visual acuity was RE 20/30 (6/9) and LE light perception. Old pigmented keratic precipitates were present in the right eye but no active uveitis. Virtually confluent lardaceous keratic precipitates covered the whole posterior corneal surface of the left eye. Posterior synechiae were also noted in the left eye. There was mild right optic nerve pallor. The left eye was treated with topical and subconjunctival steroids and mydriatics. Ten days later the right eye developed anterior chamber cells and flare, and topical treatment was started in the right eye. The keratic precipitates slowly resolved over several months. At this time examination of the left optic fundus was possible, showing a pale left optic nerve.

The patient has had several episodes of spastic paraparesis since age 46. She has also had episodes of conjugate lateral gaze palsy, spastic weakness of the right arm, and mild cerebellar ataxia of the arms, more marked on the right. Visual evoked potentials showed a considerably increased latency of the left eye. A neurologist had diagnosed her as having multiple sclerosis. The patient was HLA-B27 negative. Serology tests for syphilis and an autoantibody screen were negative. *X*-rays of the skull, chest, and lumbar spine were normal.

CASE 5

A 51-year-old Caucasian woman was referred for ophthalmological examination. Best corrected visual acuity was RE 20/40 (6/12) and LE 20/50 (6/15). Both eyes showed extensive lardaceous keratic precipitates and multiple posterior synechiae. Both optic nerves were pale. The patient was treated with topical steroids and atropine drops, with resolution of the keratic precipitates over three weeks. Mild anterior chamber inflammation persisted for nearly four months.

This patient had developed transient left leg weakness when she was 23. At age 30 she had an episode of retrobulbar neuritis. At 31 she had episodes of urinary incontinence and sensory disturbances of the hands. Later that same year she developed cerebellar ataxia of the upper limbs and right leg, with mild spasticity of all four limbs. This resolved gradually but became aggravated three years later. At age 41 she developed further worsening of her leg weakness. Laboratory studies showed a negative HLA-B27 and negative serology for syphilis and autoantibody screens. Skull, chest, and lumbar spine *x*-rays were normal. visual evoked potentials done when she was 53 were normal. A neurologist had diagnosed probable multiple sclerosis.

Discussion

The five reported patients with granulomatous uveitis had a form of clinical multiple sclerosis (Table 1). In all cases the diseases most often associated with granulomatous uveitis (tuberculosis, sarcoidosis, and syphilis) were excluded by appropriate testing. All cases had bilateral uveitis, and cases 1, 2, and 3 had pars planitis and striking iris nodules. In no case did the uveitis appear to coincide with an exacerbation of the neurological condition.

One could suppose that cases 1 to 5 may be afflicted with a disease similar to multiple sclerosis but aetiologically different from other forms of multiple sclerosis, where the uveal tract remains uninvolved. It is also possible that these patients have some combination of HL-A antigens which predispose them to develop both a uveitis and multiple sclerosis. However rare the coexistence of these two diseases further studies of such patients may help to explain a possible aetiology of multiple sclerosis.

Wuseke first noted the association of multiple sclerosis and uveitis in three patients with peripheral uveitis and multiple sclerosis.[1] Since then numerous authors have reported a similar finding.[4,7-9,11,14,15,18] Several patients have had pars planitis,[14,15] while others showed discrete foci of choroiditis.[4,11] Many patients have been described who have had sheathing of peripheral retinal veins, with or without pars planitis.[2,3,6,10,12-18] The coexistence of these two inflammatory diseases in the same patient inevitably leads to speculation as to a common aetiology, especially since the plaques of multiple sclerosis have a natural preference for a perivenous distribution. That both retina and brain are neuroectodermally derived lends support to this hypothesis.

Diseases of the central nervous system other than multiple sclerosis which may be associated with uveitis include syphilis, tuberculosis, sarcoidosis, Vogt-Koyanagi-Harada disease, Behçet's syndrome, and toxoplasmosis. We found no evidence for any of these in our patients.

One of Wuseke's patients had iris nodules of the type initially described by Koeppe[19] in patients with tuberculosis. These nodules are found at the inner pupillary margin (Fig. 1). They have also been noted in syphilitic iritis and herpes zoster iritis.[20] Our case 2

Table 1 *Patients with granulomatous uveitis and neurological disease*

Case	*Age*	*Sex*	*Neurological diagnosis*	*Eye findings*	*Comment*
1	39	F	Probable multiple sclerosis	Granulomatous anterior uveitis, iris nodules, vitritis, retinal venous sheathing	
2	50	F	Probable multiple sclerosis	Granulomatous anterior uveitis, iris nodules, vitritis, pseudoexfoliation, cystoid macular oedema	HLA-B27+
3	38	F	Multiple sclerosis	Retrobulbar neuritis, granulomatous anterior uveitis, iris nodules, vitritis	Sister with multiple sclerosis but no uveitis
4	52	F	Probable multiple sclerosis	Granulomatous anterior uveitis, retrobulbar neuritis, cystoid macular oedema	
5	52	F	Probable multiple sclerosis	Granulomatous anterior uveitis	

had a nodule on the surface of the iris stroma of the type Busacca[21] noted in patients with tuberculous lymphadenitis. Since the time of Friedenwald and Friedenwald[22] these types of iris nodules have been considered to be a sign of granulomatous uveitis, as they have also been seen in sarcoidosis and sympathetic ophthalmia, two clearly granulomatous diseases.[23] It is intriguing to note that pars planitis as described by Brockhurst *et al.*[24] is not associated with iris nodules, though it may present with 'gelatinous' exudates in the anterior chamber angle. In addition lardaceous keratic precipitates are rarely seen in pars planitis.

Our patients showed that pars planitis, traditionally considered a non-granulomatous uveitis, can present with iris nodules and lardaceous keratic precipitates, two clinical signs of granulomatous disease. Admittedly the ultimate differentiation between granulomatous and non-granulomatous disease can be made only histologically. However, in most cases the clinical picture showed should show the differences between the two. Perhaps an altered immune system in the patient with multiple sclerosis may cause granulomatous findings to appear in a disease that is normally non-granulomatous. Nevertheless these patients show that the occurrence of granulomatous uveitis should alert the ophthalmologist to the possibility of multiple sclerosis.

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References

1 Wuseke W. Seltener Augenveranderrungen bei multipler Sklerose. *Ber Dtsch Ophthalmol Ges* 1953;**58**:338-9.

2 ter Braak JWG, van Herwaarden A. Ophthalmo-encephalomyelitis. *Klin Monatsbl Augenheilkd* 1933;**91**:316-43.

3 Rucker CW. Sheathing of the retinal veins in multiple sclerosis. *Mayo Clin Proc* 1944;**19**:176-8.

4 Bucalossi A. Sulla presenza ed il significato de lesioni chorio-retiniche nella sclerosi a placche. *Atti Soc Ottal Ital* 1947;**36**: 113-20.

5 Haarr M. Periphlebitis retinae in association with multiple sclerosis. *Acta Psychiatr Scand* 1953;**28**:175-90.

6 Orban T. Beitrage zu den Augenhintergrundsveranderungen bei Sclerosis multiplex. *Ophthalmologica* 1955;**30**:387-96.

7 D'Ermo F. Su di una rare complicanza oculare della sclerosi a placche. *Boll Oculist* 1956;**35**:436-44.

8 Garde A, Tommasi M, Pellet M. A propos d'une observation anatomo-clinique d'encephalomyélite disseminée associée à une uvéite. *Rev Neurol (Paris)* 1957;**97**:139-42.

9 Garcin R. A propos de quelques observations d'uvéonevrites et en particulier d'association d'uvéite et de syndromes neurologiques du type de la sclérose en plaques. *Laval Med* 1958;**26**: 522-54.

10 Ardouin M, Feuvrier YM, Catros A, Urvoy M. La periphlébite rétinienne de la sclérose en plaques. *Rev Otoneuroophtalmol* 1960;**32**:3-8.

11 Pacurariu I, Pacurariu L. Complicatii kerao-uveale in scleroza in placi. *Oftalmologia (Buc)* 1960;**4**:39-42.

12 Tschabitscher H, Sluga-Gasse E, Schinko H. Hyperergische Erkrankungen am Auge in Rahmen von multipler Sklerose. *Wien Med Wochenschr* 1962;**112**:279-85.

13 Moller PM, Hammerberg PE. Retinal periphlebitis in multiple sclerosis. *Acta Neurol Scand* 1963;**39**(Suppl 4):263-70.

14 Archambeau PL, Hollenhorst RW, Rucker CW. Posterior uveitis as a manifestation of multiple sclerosis. *Mayo Clin Proc* 1965;**40**:544-51.

15 Breger BC, Leopold IH. The incidence of uveitis in multiple sclerosis. *Am J Ophthalmol* 1966;**62**:540-5.

16 Morse P. Retinal venous sheathing and neovascularization in disseminated sclerosis. *Ann Ophthalmol* 1975;**7**:949-52.

17 Younge BR. Fluorescein angiography and retinal venous sheathing in multiple sclerosis. *Can J Ophthalmol* 1976;**11**:31-6.

18 Bamford CR, Ganley JP, Sibley WA, Laguna JF. Uveitis, perivenous sheathing and multiple sclerosis. *Neurology (Minneap)* 1978;**28**:119-24.

19 Koeppe L. Klinische Beobachtungen mit der Nernstspaltlampe und dem Hornhautmikroskop. *Albrecht von Graefes Arch Klin Ophthalmol* 1917;**92**:115.

20 Vogt A. Weitere Ergebnisse der Spaltlampenmikroskopie des vorderen Bulbusabschnittes. *Albrecht von Graefes Arch Klin Ophthalmol* 1923;**111**:91.

21 Busacca A. Anatomische und klinische Beobachtungen der Pupillarsaumknotchen (Koeppschen Knotchen) bei Iridozyklitis. *Klin Monatsbl Augenheilkd* 1932;**88**:14.

22 Friedenwald H, Friedenwald F. Globular masses on the pupillary margin in acute circumscribed chorioretinitis: a clinical and pathological study. *Arch Ophthalmol* 1926;**55**:113.

23 Woods AC. *Endogenous inflammations of the uveal tract.* Baltimore: Williams and Wilkins, 1961.

24 Brockhurst RJ, Schepens CL, Okamura ID. Uveitis I. Gonioscopy. *Am J Ophthalmol* 1956;**42**:545-50.

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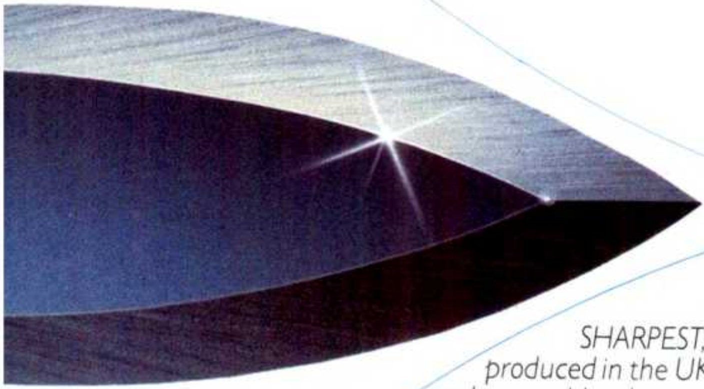

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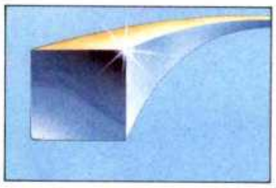

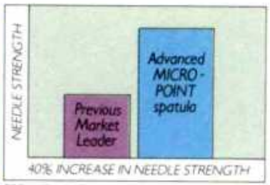

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Morphological variation of Dalén-Fuchs nodules in sympathetic ophthalmia

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SUMMARY Fifty cases of sympathetic ophthalmia were examined histologically to determine the incidence and morphology of Dalén-Fuchs nodules. At least one well-defined Dalén-Fuchs nodule was identified in 18 (36%) of the eyes examined. Three types of lesions at the level of the retinal pigment epithelium were recognised. One type was found to consist of focal hyperplasia and aggregation of retinal pigment epithelial cells. A second type, classically referred to as Dalén-Fuchs nodules, consisted of epithelioid cells and lymphocytes covered by an intact dome of retinal pigment epithelium. The third type of lesion was characterised by degeneration of the overlying retinal pigment epithelium leading to disorganisation of the Dalén-Fuchs nodule and possible release of their contents into the subretinal space. Our study demonstrated that Dalén-Fuchs nodules in sympathetic ophthalmia vary in their morphological appearance as determined by light microscopy.

Isolated nodular collections of cells lying between Bruch's membrane and the retinal pigment epithelium, in association with sympathetic ophthalmia, are classically referred to as Dalén-Fuchs nodules.[1] The morphologic appearance of the nodular lesions was originally described in 1881 by Brailey[2] as 'small globular aggregations of unpigmented cells, in or upon the pigment epithelial layer . . . by means of which small tracts of the ciliary retina may be raised in an arch-like manner.' The classic studies by Dalén[3] in 1904 and Fuchs[4] in 1905 showed that these hemispherical nodular lesions consisted primarily of epithelioid cells, lymphocytes, and metaplastic cells from the retinal pigment epithelium.

Although the Dalén-Fuchs nodule is a characteristic pathological feature of sympathetic ophthalmia, found in both sympathising and exciting eyes, it is not pathognomonic for this entity. Dalén-Fuchs nodules have also been reported in sarcoidosis, tuberculosis, and the Vogt-Koyanagi-Harada syndrome.[5 6]

The purpose of this study is to describe the morphological variation of Dalén-Fuchs nodules in sympathetic ophthalmia.

Materials and methods

Fifty histologically verified cases of sympathetic ophthalmia obtained from the pathology files of the Estelle Doheny Eye Foundation, Los Angeles, California, USA, and from cases referred to the Doheny Sympathetic Ophthalmia Study were evaluated by light microscopy to determine the incidence and morphological features of Dalén-Fuchs nodules. In 48 cases the exciting eye was examined histologically. In two unrelated cases the sympathising eye was examined histologically.

Results

INCIDENCE

The presence of at least one well-defined Dalén-Fuchs nodule was confirmed in 18 (36%) cases. This figure represents a conservative estimate, because serial sections were not available in all cases.

MORPHOLOGICAL VARIATION OF DALÉN-FUCHS NODULES

The Dalén-Fuchs nodule is recognised typically as a hemispherical mound primarily consisting of epithelioid cells and occasional lymphocytes beneath the

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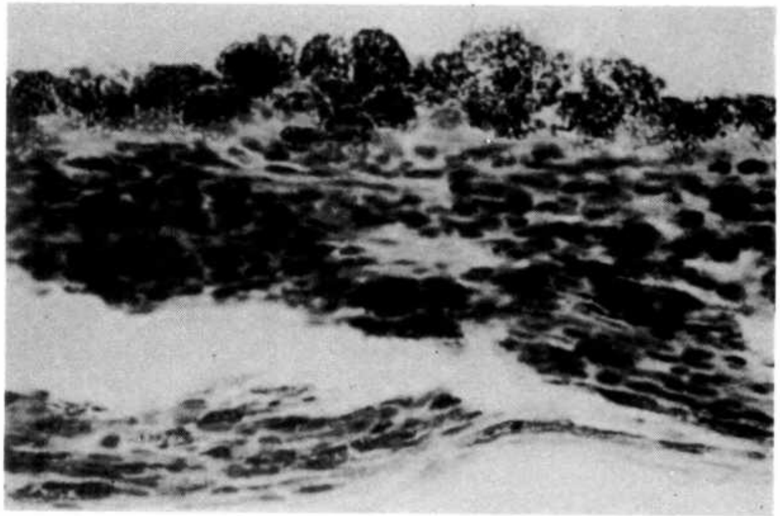

Fig. 1 *Focal hypertrophy and aggregation of the retinal pigment epithelium suggestive of early Dalén-Fuchs nodule formation. (Haematoxylin and eosin, ×135).*

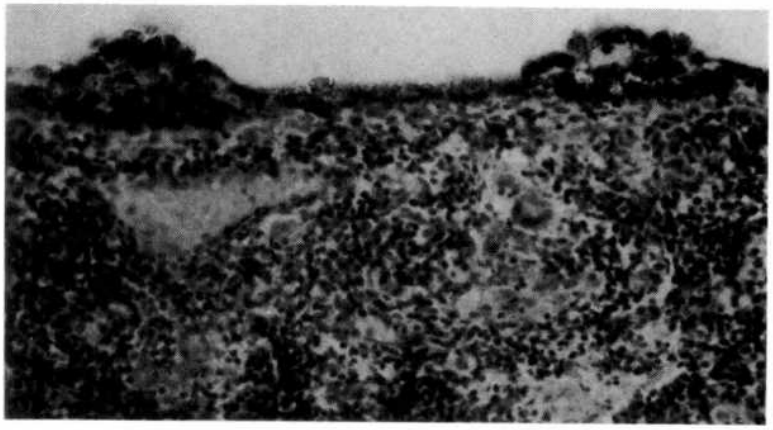

Fig. 2 *Diffuse granulomatous uveitis with obliteration of the choriocapillaris and focal mounds of retinal pigment epithelial cells. (Haematoxylin and eosin, ×50).*

retinal pigment epithelium. Careful evaluation of our material revealed a morphological spectrum of lesions occurring along the retinal pigment epithelium.

The first type of lesion providing the earliest indication of Dalén-Fuchs nodule formation consists of focal hyperplasia and aggregation of retinal pigment epithelial cells (Fig. 1). The retinal pigment epithelial cells form small mounds or localised areas of stratification (Fig. 2).

The second type of lesion is characterised by the presence of well defined and closely packed collections of epithelioid cells underlying a dome of retinal pigment epithelium. These lesions are classically interpreted as Dalén-Fuchs nodules (Fig. 3). Metaplastic cells from the retinal pigment epithelium, lymphocytes, and giant cells may occasionally be found within this nodular structure (Fig. 4).

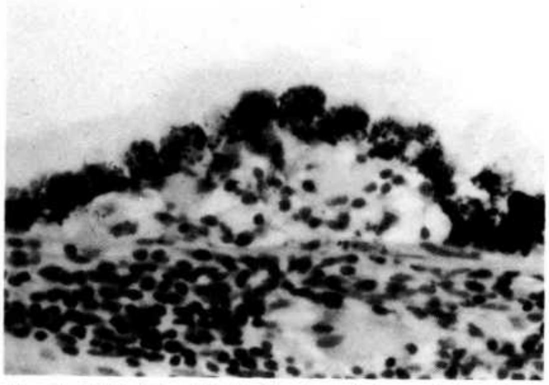

Fig. 3 *Well-defined Dalén-Fuchs nodule consisting of lymphocytes and epithelioid cells beneath a dome of retinal pigment epithelial cells. (Haematoxylin and eosin, ×108).*

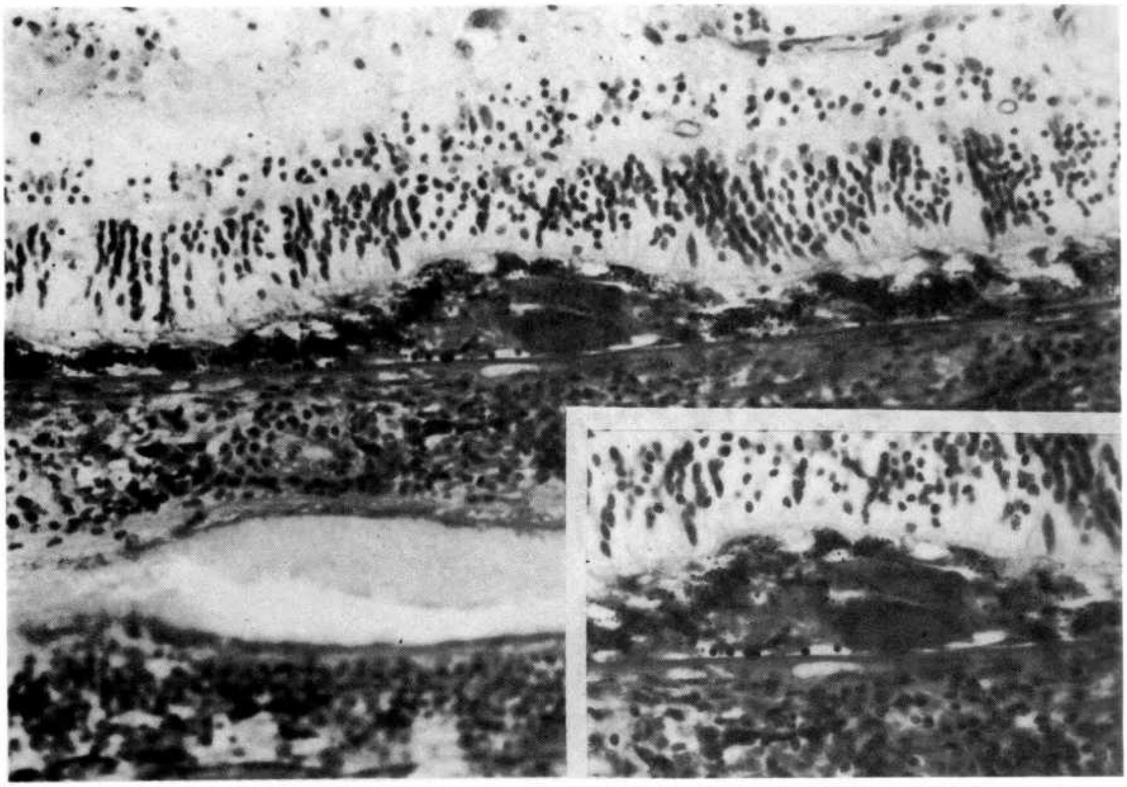

Fig. 4 *Dalén-Fuchs nodule containing epithelioid cells and a giant cell. The dome of retinal pigment epithelium appears to have undergone degeneration. (Haematoxylin and eosin, ×40; inset ×108).*

In the third type of lesion the retinal pigment epithelial dome of the Dalén-Fuchs nodule degenerates. The retinal pigment epithelium disappears first at the apex of the nodule and then completely. Degeneration of the retinal pigment epithelial dome may allow cells of the Dalén-Fuchs nodule to separate from each other and be released into the subretinal space (Fig. 5). All three types of lesions described may occur in the same case.

A clear relationship between duration of disease and morphological type of Dalén-Fuchs nodule could not be established; the three types of lesions described were found in eyes enucleated early and late in the course of sympathetic ophthalmia. Eyes with Dalén-Fuchs nodules that were enucleated relatively early in the course of sympathetic ophthalmia tended to have nodules limited to an area anterior to the equator (Table 1). Generalised involvement of Dalén-Fuchs nodules along the entire length of retinal pigment epithelium was found primarily in eyes enucleated late in the course of sympathetic ophthalmia.

Table 1 *Location of Dalén-Fuchs nodules*

Location of Dalén-Fuchs nodules	*Interval of time in weeks from symptoms to enucleation (18 cases)*		
	0–3	*4–11*	*12+*
Anterior to equator	5	2	0
Posterior to equator	0	3	1
Generalized involvement	1	2	4*

*Including two sympathising eyes.

Discussion

Our present study showed that Dalén-Fuchs nodules in sympathetic ophthalmia vary in their morphological appearance as determined by light microscopy. The earliest histological finding suggestive of Dalén-Fuchs nodule formation was focal disturbance of the retinal pigment epithelium with cellular hyperplasia and aggregation. The Dalén-Fuchs nodule appears to enlarge as a result of epithelioid cells and lymphocytes accumulating beneath a dome of retinal pigment epithelium.[4] Ultrastructural studies indicate the pigment epithelial cells forming the dome of the Dalén-

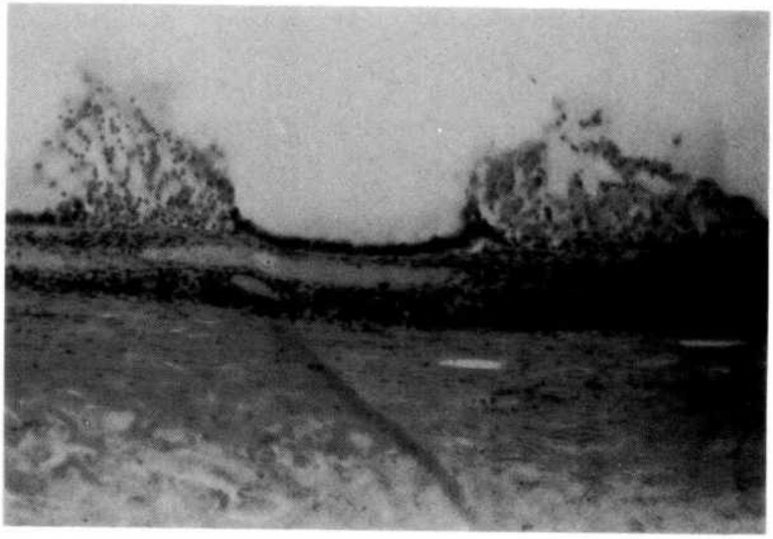

Fig. 5 *Dissolution of Dalén-Fuchs nodules with apparent release of their contents into the subretinal space. Well defined Dalén-Fuchs nodules were present in the same section. (Haematoxylin and eosin, ×50).*

Fuchs nodule elongate in a vertical direction to reach Bruch's membrane.[7] As a result, a complex cage-like framework is formed within the nodule.[7 8] Metaplastic cells from the retinal pigment epithelium, lymphocytes, and giant cells may occasionally be found within the Dalén-Fuchs nodule. Ultimately, the retinal pigment epithelial dome degenerates and disappears. Terms such as 'autolysis'[1] and 'bursting'[4] have been used by other investigators to describe the histological appearance of Dalén-Fuchs nodules in this form. The spectrum of morphological changes occurring at the level of the retinal pigment epithelium is consistent with Ernst Fuchs's original hypothesis that Dalén-Fuchs nodules undergo an evolutionary sequence of development.[4] However, further evidence is necessary to confirm this hypothesis.

The source of cells that collect within the Dalén-Fuchs nodule is controversial. By means of detailed electron microscopic study Font and associates[8] found that the vast majority of cells within Dalén-Fuchs nodules represented transformed retinal pigment epithelium. They concluded that epithelioid cells in Dalén-Fuchs nodules were derived from retinal pigment epithelial cells. However, using immunological and ultrastructural analysis Jakobiec and associates[9] found that Dalén-Fuchs nodules were composed of a mixture of histiocytes, lymphocytes, and depigmented epithelial cells. These authors concluded that many of the cells comprising Dalén-Fuchs nodules are of bone marrow origin. Our observations suggested that the cellular composition of Dalén-Fuchs nodules may vary according to the morphological form sampled for analysis: Dalén-Fuchs nodules sampled early in their development may show a predominance of metaplastic epithelial cells whereas, mature Dalén-Fuchs nodules may show a mixture of cellular components.

Similarly, the correlation between fundus angiographic findings and Dalén-Fuchs nodules has been controversial.[10] Lewis and colleagues[11] presented fluorescein angiographic findings in a sympathising eye that showed early blockage of background fluorescence by multiple discrete lesions at the level of the retinal pigment epithelium; these lesions gradually stained during the later phases of the angiogram. Histopathological examination of the exciting eye showed multiple areas of choriocapillaris obliteration by inflammatory cells and overlying Dalén-Fuchs nodules. Sharp and coworkers[12] reported a case with comparable histopathological and angiographic findings. In contrast Segawa and Matsuoka[13] showed fine, hyperfluorescent dots in the posterior pole of a sympathising eye during the arterial phase; these dots corresponded in dimension with Dalén-Fuchs nodules in the exciting eye. Spitznas[14] and other investigators[15 16] described similar angiographic findings.

The morphological spectrum of Dalén-Fuchs nodules suggests that it may present a variable angiographic appearance. Blockage of choroidal fluorescence may occur when an intact dome of retinal pigment epithelium contains the cellular elements of the Dalén-Fuchs nodule; the collection of densely packed epithelioid cells covered by tight intercellular junctions of the retinal pigment epithelium provides an effective block of underlying choroidal fluorescence.[11] Gradual accumulation of fluorescein into Dalén-Fuchs nodules may produce focal hyperfluorescence.[12] However, degeneration of the retinal pigment epithelium overlying the Dalén-Fuchs nodule may allow fluorescein dye to permeate a focus in the retinal pigment epithelium and gradually accumulate in the subretinal space.[15 16] Variation in the angiographic appearance of Dalén-Fuchs nodules may therefore be related to its fluorescein permeability and morphologic form.

We concluded that the morphological spectrum of Dalén-Fuchs nodules may explain its variable histological and fluorescein angiographic presentation. The observations of our study provides a background for additional clinicopathological correlation of Dalén-Fuchs nodules in sympathetic ophthalmia.

We thank Milton Reynard and Nancy J Cramer for technical assistance.

References

1 Duke-Elder S, Perkins ES. Diseases of the uveal tract. In: Duke-Elder S, ed. *System of ophthalmology*. London: Kimpton, 1966; **9**: 581–3.

2 Brailey WA. On the pathology of sympathetic ophthalmitis. *Trans Int Med Congs*, seventh session, 1881; **3**: 35–9.

3 Dalén A. Zur kenntnis der sogenannten Choroiditis sympathetica. *Mitt Augenklinik des Carolin Med Chirurg Instit z Stockholm* 1904; **6**: 1–22.

4 Fuchs E. Über sympathisierende Entzündung (nebst Bemerkungen über seröse traumatische Iritis). *Albrecht von Graefes Arch Klin Ophthalmol* 1905; **61**: 365–456.

5 Campinchi R, Faure JP, Bloch-Michel E, Haut J. *Uveitis: Immunologic and allergic phenomenon*. Springfield: Thomas, 1963; **5**: 160.

6 Greer CH. *Ocular pathology*. Oxford: Blackwell, 1979; **3**: 40.

7 Ishikawa T, Ikui H. The fine structure of the Dalén-Fuchs nodule in sympathetic ophthalmia. *Jpn J Ophthalmol* 1972; **16**: 254–65.

8 Font RL, Fine BS, Messmer E, Rowsey JF. Light and electron microscopic study of Dalén-Fuchs nodules in sympathetic ophthalmia. *Ophthalmology* 1982; **89**: 66–75.

9 Jakobiec FA, Marboe CC, Knowles DM, *et al*. Human sympathetic ophthalmia. An analysis of the inflammatory infiltrate by hybridoma-monoclonal antibodies, immunochemistry, and correlative electron microscopy. *Ophthalmology* 1983; **90**: 76–95.

10 Puliafito CA, Smith TR, Packer AJ, Albert DM. Sympathetic uveitis. *Ophthalmology* 1980; **87**: 355–8.

11 Lewis ML, Gass JDM, Spencer WH. Sympathetic uveitis after trauma and vitrectomy. *Arch Ophthalmol* 1978; **96**: 263–7.

12 Sharp DC, Bell RA, Patterson E, Pinkerton RMH. Sympathetic ophthalmia. Histopathologic and fluorescein angiographic correlation. *Arch Ophthalmol* 1984; **102**: 232–5.

13 Segawa K, Matsuoka N. Sympathetic ophthalmia. A comparative fluorographic and electron microscopic study. *Jpn J Ophthalmol* 1971; **15**: 81–7.

14 Spitznas M. Fluoreszenzangiographie der sympathischen Ophthalmia. *Klin Monatsbl Augenheilkd* 1976; **169**: 195–200.

15 Dreyer WB, Zegarra H, Zakov ZN, Gutman FA. Sympathetic ophthalmia. *Am J Ophthalmol* 1981; **92**: 816–23.

16 Kayazawa F. A case of sympathetic uveitis. *Ann Ophthalmol* 1980; **12**: 1106–8.

British Journal of Ophthalmology, 1985, **69**, 202–204

Seasonal variation of acute anterior uveitis: differences between HLA-B27 positive and HLA-B27 negative disease

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SUMMARY One hundred and seventy-five consecutive patients with acute anterior uveitis (AAU) were examined over a 24-month period. There was a significantly increased incidence of AAU during the months August to December ($p<0·05$). This increase was confined predominantly to the HLA-B27 negative group of patients ($p<0·01$). There was no significant monthly difference in incidence between males and females, between patients with first or recurrent attacks, or between patients with and without arthritis. These results suggest that seasonal environmental factors may play a role in the production of HLA-B27 negative AAU.

The possibility that infection may trigger episodes of acute anterior uveitis (AAU) has been the subject of speculation and investigation for some years. In a small number of cases AAU may develop after an acute enteric infection with salmonella,[1] shigella,[2] or *Yersinia enterocolitica*.[3] A genetic predisposition to the development of AAU is known. About half of all cases carry the tissue antigen HLA-B27.[4] There is a strong association of AAU with various rheumatic diseases known as the seronegative spondylarthropathies, and most patients with these spondylarthropathies and those who develop AAU after enteric infection carry the HLA-B27 antigen.

Many ophthalmologists have had the impression that there are seasonal fluctuations in the incidence of AAU. Seasonal fluctuations in the frequency of a disease, particularly an acute inflammatory process such as AAU, suggest that an environmental factor may be involved in initiating or modulating the disease. It was therefore decided to examine the month of onset of all recorded episodes of AAU in a prospective, consecutive series of patients presenting over a 24 month period. The aim of the study was to determine if there was a seasonal pattern to AAU, and in particular to determine if there was any specific relationship with other variables such as HLA tissue type, presence of arthritis, sex, and whether this was associated with first or recurrent attacks of AAU.

Patients and methods

Patient selection. One hundred and seventy-five consecutive patients with AAU were seen in the uveitis clinic over the 24-month period from April 1981 to March 1983. Patients with chronic uveitis (that is, those requiring more than three months of treatment) or patients with granulomatous or posterior uveitis were excluded from the study. Twenty-nine of these patients had earlier recorded and confirmed episodes of AAU with the month of onset available from the hospital records. Three patients had two episodes each during the study. In all 207 episodes were included. All patients were examined for HLA-A and B loci with the standard two-stage microlymphocytotoxicity assay.

Statistical analysis. Statistical analysis was carried out by χ^2 with Yates's correction for small numbers. Analysis of the results was carried out in two ways. In the first instance a 12-cell χ^2 analysis for incidence of AAU per month was examined. The null hypothesis was that there should be no excessive fluctuations in any month. This form of statistical analysis makes no attempt to examine any particular month but merely indicates whether there was a significant deviation

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from the expected monthly incidence. In the second analysis the patients were divided on the basis of HLA-B27 tissue type, sex, presence of arthritis or first or recurrent attacks, and again 12 cell χ^2 tables were constructed.

Results

The results showed a statistically significant deviation from the expected observations when all AAU patients were examined (Fig. 1), $\chi^2 = 21{\cdot}3$, df = 11, $p<0{\cdot}05$). When patients were divided on the basis of HLA-B27 tissue typing, the deviation was found to occur only in the B27 negative patients (Fig. 2), ($\chi^2 = 26{\cdot}0$, df = 11, $p<0{\cdot}01$). Inspection of the individual χ^2 values in each cell of the table in both these studies showed that much of the largest contribution to the total came from the months of August to November, and particularly November itself. Although there was a slight increase in the incidence of HLA-B27 positive AAU in the four months from August to November inclusive (Fig. 3), there was no significant deviation from the expected results in this patient group. There was no statistically significant monthly difference in incidence observed in males or females, in patients with first or recurrent attacks, or in patients with and without arthritis.

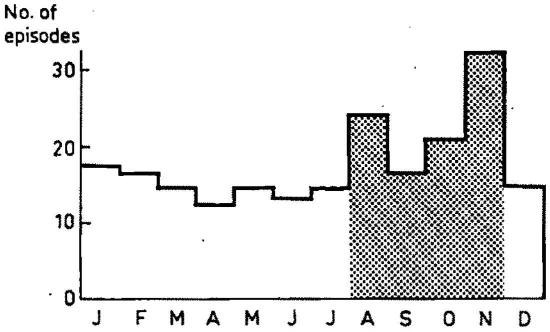

Fig. 1 *Month of onset of 207 cases of AAU in 175 patients.*

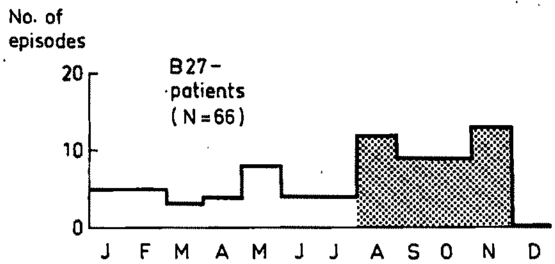

Fig. 2 *Month of onset of AAU in HLA-B27 negative (B27–) patients.*

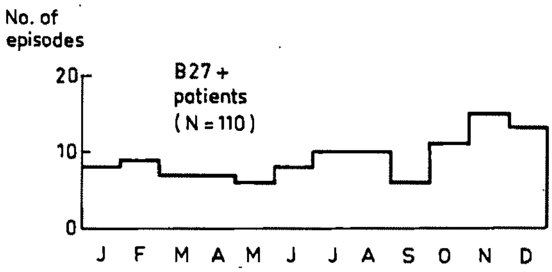

Fig. 3 *Month of onset of AAU in HLA-B27 positive (B27+) patients.*

Discussion

Our results showed a significant deviation of incidence of episodes of HLA-B27 negative AAU during the southern hemisphere spring months in a prospective group of patients studied in Melbourne. The hypothesis under test was not a priori related specifically to any particular month or group of months.

Although examination of the tables showed that the largest contribution to the χ^2 value came from the spring months, it is not possible statistically to analyse these data further. To confirm this observation it would be necessary to examine a new series of patients, and investigate the specific hypothesis that there is a seasonal peak in HLA-B27 negative AAU during the spring months.

A seasonal change in hospital referral patterns appears unlikely to be the reason for the change. Firstly, there is no obvious specific reason for an increase in hospital referrals at that time such as holiday periods or unavailability of private ophthalmological treatment. Secondly, the observation that this increase in patients occurred in a subgroup of patients who have distinctive clinical and immunological features[5-7] makes it more likely that the increase is a real observation and an important aetiological factor in the production of these diseases.

The most likely explanation for the seasonal fluctuation is the effect of a common environmental factor acting on the B27 negative subgroup of AAU patients.[8] The possibilities include infective agents, dietary changes, or possibly seasonal allergic phenomena.

Apart from the small number of cases of AAU associated with Gram-negative enteric pathogens the evidence for infective factors in idiopathic AAU is preliminary. Recent reports have implicated faecal carriage *Klebsiella pneumoniae* with the development of AAU in patients with ankylosing spondylitis.[9-10] We have recently observed a similar increase in AAU faecal carriage of klebsiella in a prospective series of unselected AAU patients.[5] In the main, however, it has been HLA-B27 positive

AAU patients who have been shown to have an association with Gram-negative bacteria.

An alternative explanation for the spring excess of AAU may be that the B27 negative subgroup of patients is affected by seasonal allergic factors. The spring months are the time of maximum pollen and grass related allergic phenomena. A recent report has suggested that serum IgE levels are raised in HLA-B27 negative AAU patients.[7] These factors are currently under investigation in HLA-B27 negative associated AAU.

We are grateful to the many ophthalmologists, particularly Dr B Coote, who referred patients to us for investigation. These studies were supported by a grant from the OPSM Foundation, the Austin Hospital Research Foundation, and a research project grant from the Royal Victorian Eye and Ear Hospital. We are also grateful to Janet Finlayson, who typed the manuscript.

References

1 Saari KM, Vilpulla A, Lassus A, Leirisalo M, Saari R. Ocular inflammation in Reiter's disease after salmonella enteritis. *Am J Ophthalmol* 1980; **90**: 63-8.

2 Paronen I. Reiter's disease; a study of 344 cases observed in Finland. *Acta Med Scand* 1948; **131**(suppl 213): 1-114.

3 Saari KM, Laitinen O, Leirisalo M, Saari R. Ocular inflammation associated with *Yersinia* infection. *Am J Ophthalmol* 1980; **89**: 84-95.

4 Brewerton DA. HL-A27 and acute anterior uveitis. *Ann Rheum Dis* 1975; **34**(suppl 1): 33-5.

5 White L, McCoy R, Tait B, Ebringer R. A search for Gram-negative enteric micro-organisms in acute anterior uveitis: association of klebsiella with recent onset of disease, HLA-B27 and B7 CREG. *Br J Ophthalmol* in press.

6 McCoy R, White LF, Tait B, Ebringer R. Serum immunoglobulins in acute anterior uveitis. *Br J Ophthalmol* in press.

7 Wakefield D, Easter J, Robinson P, Penny R. Immunological features of HLA-B27 anterior uveitis. *Aust J Ophthalmol* 1983; **11**: 15-9.

8 Barker DJP, Rose G. *Epidemiology in medical practice.* 2nd ed. London: Churchill-Livingstone, 1979: 70.

9 Ebringer R, Cawdell D, Ebringer A. *Klebsiella pneumoniae* and acute anterior uveitis in ankylosing spondylitis. *Br Med J* 1979; **i**: 383.

10 Willshaw H, Eastmond C. Role of environmental factors in uveitis. *Trans Ophthalmol Soc UK* 1979; **99**: 160-2.

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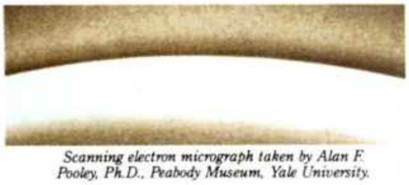

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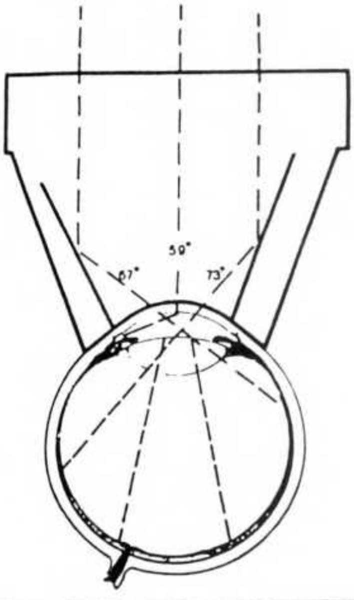

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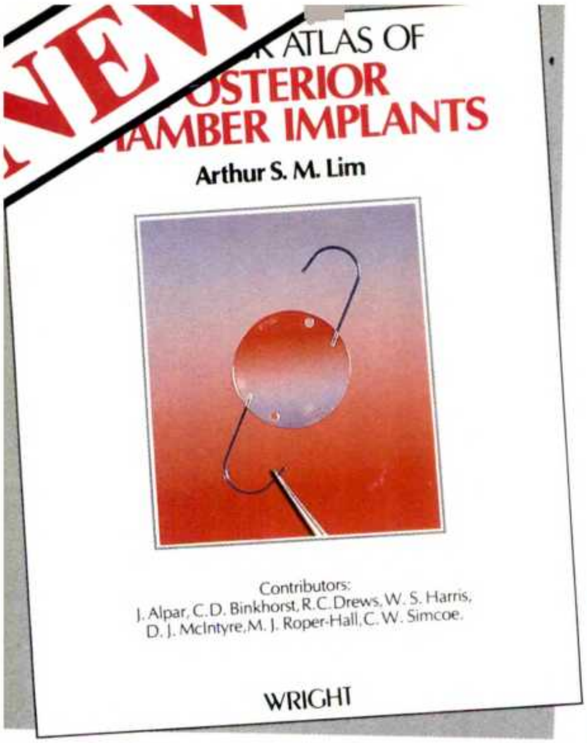
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Pupillary constriction to darkness

MICHAEL J PRICE, H STANLEY THOMPSON, G FRANK JUDISCH, AND JAMES J CORBETT

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SUMMARY Patients with congenital achromatopsia and congenital stationary night blindness have been known to show a transient pupillary constriction to darkness. We examined 50 normal subjects and 108 patients with retinal and optic nerve dysfunction to see if any had an initial pupillary constriction to darkness. We used a new infrared television apparatus. Four patients with congenital stationary night blindness, four with achromatopsia, two with bilateral optic neuritis, and one with dominant optic atrophy showed the phenomenon. In the patients who showed this unusual pupillary response to darkness it was the first observable event every time the lights were turned off. The constriction could usually be seen with a handlight, and it was similar in latency to the normal pupillary dilatation to darkness. Pupillary constriction to darkness is a clinically valuable sign that can be used in the detection of congenital retinal disease in children with poor vision.

Children with congenital stationary night blindness and congenital achromatopsia have been found to have unusual pupillary reactions. When the lights are turned out their pupils briefly constrict before they dilate in the customary way.[1 2] Patients with congenital achromatopsia have defective receptor elements and have photophobia, decreased visual acuity, nystagmus, and an abnormal photopic electroretinogram.[3] On the other hand congenital stationary night blindness represents a miswiring of retinal signals, in which the pigment kinetics are normal.[4] Patients with this condition are night blind and have a reduced scotopic electroretinogram with raised dark adaptation.[5 6] Although differing in their retinal abnormalities congenital stationary night blindness and congenital achromatopsia are somehow linked, since they both show a transient pupillary constriction to darkness. Is this pupillary phenomenon limited to congenital stationary night blindness and congenital achromatopsia? Can it be used to aid in the separation of congenital retinal disease from optic nerve disease in patients with poor vision? To assess the incidence and utility of this phenomenon as a diagnostic sign we compared a group of patients with retinal and macular degenerations, both hereditary and involutional, with patients seen in a neuro-ophthalmic outpatient clinic. All recordings were made with a new infrared television technique. An animal model of congenital stationary night blindness[7] was also studied.

Subjects and methods

All patients were selected from the Neuro-ophthalmology, Ophthalmic Genetics, and Retina Clinics of the University of Iowa. In addition, patients with congenital stationary night blindness and congenital achromatopsia were recalled for assessment. Patients with other hereditary retinal diseases, including retinitis pigmentosa and Stargardt's disease, and patients with senile macular degeneration also had their pupillary reactions assessed by infrared pupillometry. Patients with demyelinating, compressive, traumatic, endocrine, and toxic optic neuropathies were similarly evaluated. The pupils of 50 normal volunteers were examined by the same technique.

A positive result was defined as a visible pupillary constriction in darkness that was consistently present each time the lights were turned out. This was, of course, much easier to see with the television apparatus, which provided magnified images of the pupils that did not disappear in the dark. The responses were recorded for later analysis.

Patients with darkness constriction of the pupil were also tested by the Farnsworth-Munsell 100 hue test, the Lanthony colour test, and for dark adaptation. Photopic, scotopic, and flicker electroretino-

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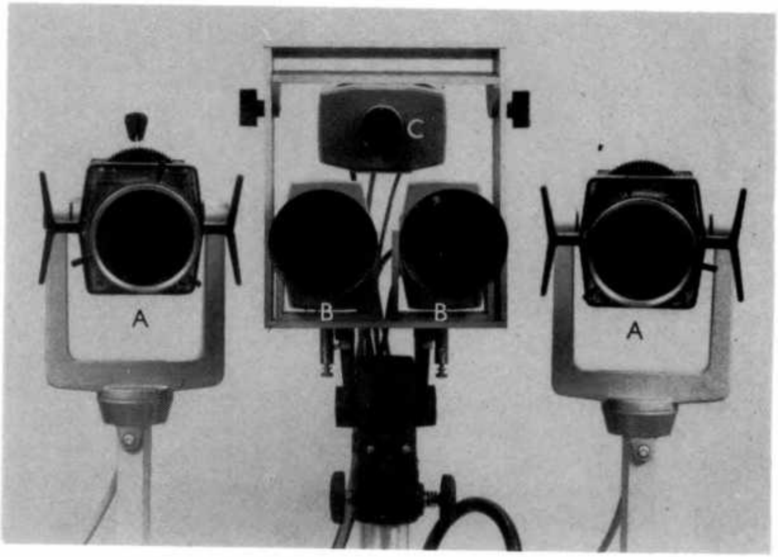

Fig. 1 *Infrared television apparatus. Two cameras* B *sensitive to infrared light are directed at the eyes. A third camera* C *is used to provide an indication of room illumination. Two sources of infrared light* A *are used for illumination.*

grams were done, with a Burian-Allen electrode with bipolar leads. A reference electrode was placed on the forehead. After 15 minutes of dark adaptation single flashes of intensity 1 and 16 were presented via a Ganzfeld stimulus from a Grass photostimulator (PS-2). Under photopic conditions, with a background light of 34·26 cd/m^2, flashes of intensity 1 and 4 were presented. Flashes at intensity 16 with a frequency of 30 Hz were then used. The frequency band was DC to 1 kHz. Individual tracings were displayed on the average (model 604C, University of Iowa) and the amplitudes and latencies were determined by means of cursors with a numbered display.

All measurements of pupillary diameter were made directly from the video monitor screen with the use of calipers. Frame by frame analysis was made for the three seconds before the lights were turned out, and the measurements of the pupil size in darkness were continued until the pupil diameter no longer increased. Two sample measurements were made for each patient and then averaged to derive the curve of the pupillary response to darkness. The mean duration and amplitude were determined from all the recorded curves for the patients in each group. The frame rate for recording was 30 frames/second. Therefore latency determination necessarily varied by ± 33 ms. The corneal diameter was estimated for each patient to determine an approximate proportional pupil size. We used fluorescent room lighting. When the lights were turned off, there was an abrupt drop in illumination. Accommodation was controlled by the patient fixing his gaze on a target and by our monitoring both eyes on the screen for any convergence movement.

The apparatus for infrared pupillometry consisted of three cameras (two RCA models 2012/M and one model 2012) (Fig. 1).Each eye had its own camera with a 135 mm low light television lens with a 20 mm extension tube and a Kodak 25 red filter (Figs. 2 A, B). These two cameras had Ultricon (RCA) pickup tubes, which are highly sensitive in the infrared light range. The third camera had a standard Vidicon tube behind a 16 mm lens without filters. It was used as an indicator of the surrounding illumination. Two light sources (Burton Medical lights), each with Kodak filter 87C, provided the infrared light. A Panasonic 9-inch (23-cm) black and white television monitor (model WV5360) displayed the output of all three cameras on the screen simultaneously. This was done with two video splitters (RCA V270SP). Fig. 2 is a photograph of the images taken directly off the screen. All images were recorded on a Sony 3/4-inch

Table 1 *Pupillary response to darkness in 108 patients*

Diagnosis	*Number of patients*	
	Normal dilatation	*Darkness constriction*
Compressive optic neuropathy	8	0
Congenital achromatopsia	2	4
Congenital stationary night blindness	5	4
Dominant optic atrophy	7	1
Graves's optic neuropathy	4	0
Leber's optic neuropathy	3	0
Optic neuritis	21	2
Papilloedema	4	0
Retinitis pigmentosa	11	0
Senile macular degeneration	26	0
Stargardt's disease	3	0
Traumatic optic neuropathy	3	0

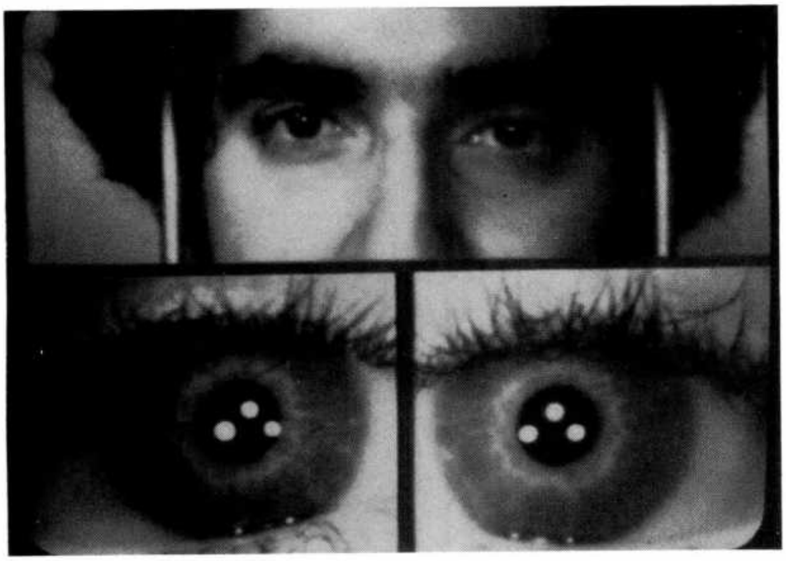

Fig. 2A *The upper photograph of the television screen was taken in room light. Part of the patient's face is visible at the top of the screen. A magnified view of each pupil is displayed in the lower half of the screen by dividing and redividing the screen with video splitters.*

(19-mm) cassette recorder/player (model VO5600). All the cameras were adjustable, and the entire system was mounted on a mobile trolley.

The Pearl mutant mouse phenotype has been described as a possible model for human congenital stationary night blindness.[7] The hypopigmented mutant Pearl mouse has defective dark adaptation but no associated photoreceptor degeneration. Each mouse was tested for pupillary constriction to darkness with an infrared sensitive television camera attached to a slit-lamp.

Results

In all, 158 patients were examined for a pupillary constriction to darkness. None of the 50 normal volunteers (ages 5-70) showed the phenomenon. Table 1 lists 108 patients with optic nerve or retinal dysfunction. Eleven patients showed pupillary constriction to darkness—eight with hereditary retinal disease and three with optic nerve disease.

Normal pupillary response. Fig. 3 shows the customary dilatation to darkness in three normal

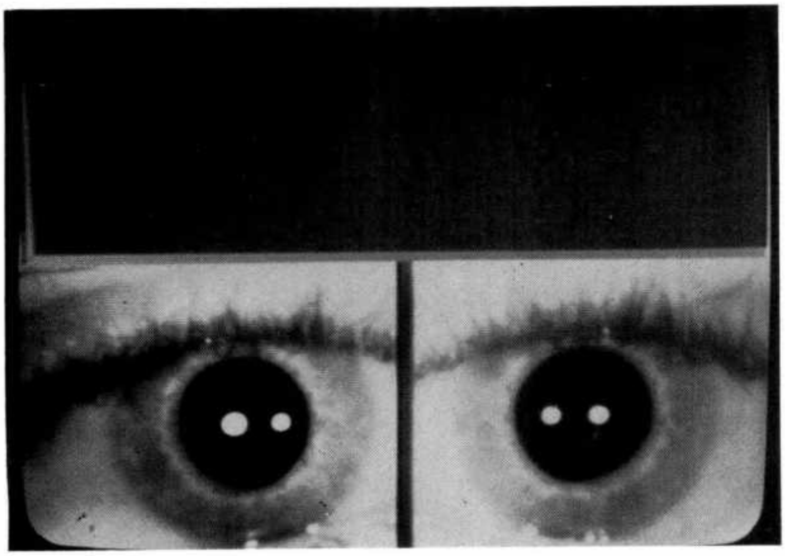

Fig. 2B *When the room lights are out* B *the patient's face is no longer visible, but the images of the pupils remain.*

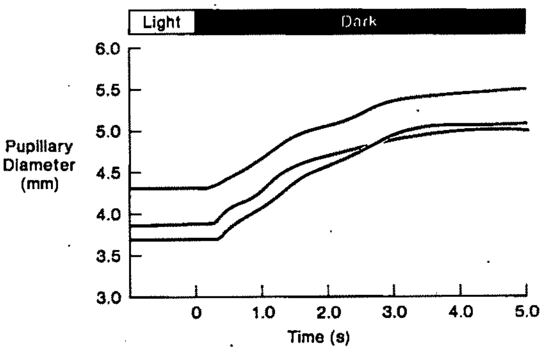

Fig. 3 *Pupillary responses in three normal subjects. The lights were turned out at the zero point on the time scale. No initial constriction can be seen.*

patients. The latency of this dilatation is in the 250-300 ms range, and the dilatation begins to level off after three seconds. There is no initial constriction.

Congenital stationary night blindness patients. Table 2 summarises the data of the patients with congenital stationary night blindness. Four patients showed pupillary constriction to darkness (patients 1-4). Their ages ranged from 10 to 26 years. Five patients aged from 6 to 30 years with congenital stationary night blindness did not show darkness constriction (patients 5-7, 17, 18). Both groups had reduced visual acuity and were night-blind and myopic to a comparable degree. There was no difference in their levels of dark adaptation, and their electroretinograms were of either the Schubert-Bornschein or the Riggs type.[5 6] In those patients with congenital stationary night blindness whose pupils constricted the constriction was the first observable event after the lights were turned off (Fig. 4). The average amplitude of pupillary constriction in this group was 1·0 mm, and the mean latency to onset of

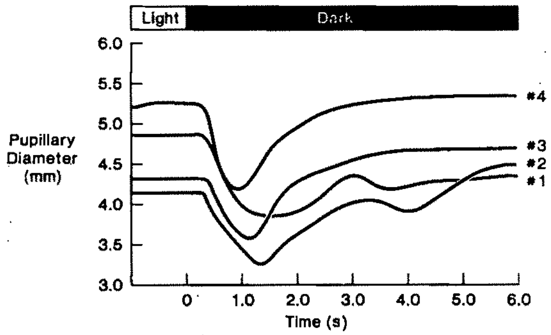

Fig. 4 *Pupillary constriction to darkness in four patients with congenital stationary night blindness showing darkness constriction of the pupil.*

Table 2 *Patients with congenital stationary night blindness*

Patient	*Age (yr)*	*Snellen acuity*		*Nystagmus*	*Refractive error*		*Colour vision*	*Dark adaptation (log units)*	*Photopic ERG*	*Flicker ERG*	*Scotopic ERG*	*Pupillary constriction to darkness*
		OD	*OS*		*OD*	*OS*						
1	20	20/50	20/50	Present	−7·25	−7·00	Normal	Raised 2·5	Reduced	Normal	Type 2	Present
2	10	20/50	20/70	Present	−14·50	−15·50	Normal	Raised 2·0	Reduced	Normal	Type 1	Present
3	24	20/40	20/40	Absent	−5·00	−4·75	Normal	Raised 2·5	Reduced	Normal	Type 1	Present
4	26	20/25	20/25	Absent	−1·75	−0·50	Normal	Raised 3·0	Normal	Normal	Type 1	Present
5	13	20/20	20/25	Absent	−3·75	−4·25	Normal	Raised 4·0	Normal	Normal	Type 1	Absent
6	6	20/80	20/70	Present	−11·00	−11·00	Normal	Raised 3·0	Reduced	Normal	Type 2	Absent
7	8	20/40	20/200	Present	−3·25	−3·00	Not done	Raised 3·0	Reduced	Normal	Type 1	Absent
17	30	20/300	20/300	Present	−4·50	−5·00	Normal	Raised 2·5	Reduced	Normal	Type 2	Absent
18	7	20/300	20/400	Present	−7·25	−7·25	Not done	Raised 3·5	Reduced	Normal	Type 1	Absent

Type 1 refers to the Schubert-Bornschein[5] form. Type 2 to the Riggs[6] form.

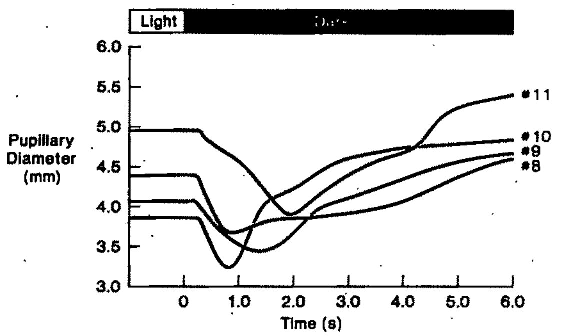

Fig. 5 *Four patients with congenital achromatopsia showing an initial constriction to darkness followed by normal dilatation.*

constriction was 280 ms. The duration of the constriction in response to darkness (the time from the initial constriction to return to the predarkness pupil diameter) averaged 3·3 s. One patient's eyes (No 1) remained constricted for seven seconds. The latency of a normal subject's pupillary dilatation to darkness under these same conditions is similar to the latency of the pupillary constriction shown by patients with congenital stationary night blindness (250-300 ms). Five patients with congenital stationary night blindness (Nos 5-7, 17, 18) showed completely normal dilatation of the pupil to darkness. Pupillary responses to light and to near targets were normal in all nine patients.

Congenital achromatopsia patients. Table 3 summarises the patients with congenital achromatopsia. There were four patients aged 10 to 32 years who showed a darkness constriction of the pupil (patients 8-11). There was an initial constriction after the onset of darkness with a mean latency of 285 ms (Fig. 5). The average amplitude of constriction was 0·9 mm, and the mean duration was 3·0 s. Only one patient (no. 10) had a very short duration of constriction of

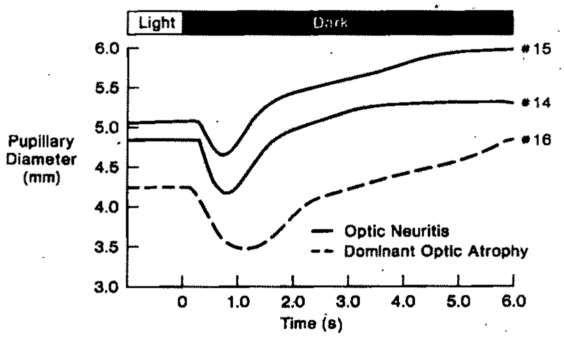

Fig. 6 *Two patients with optic neuritis* (solid lines) *and one with dominant optic atrophy* (broken lines) *showing pupillary constriction to darkness.*

Table 3 *Patients with congenital achromatopsia*

Patient	*Age (yr)*	*Snellen acuity*		*Photophobia*	*Nystagmus*	*Colour vision*	*Fundus appearance*	*Photopic ERG*	*Flicker ERG*	*Scotopic ERG*	*Pupillary constriction to darkness*
		OD	*OS*								
8	32	20/200	20/200	Present	Present	Absent	Pigment mottling in macula, absent foveal reflex	Reduced	Absent	Mildly reduced	Present
9	31	20/400	20/400	Present	Present	Absent	Absent foveal reflex	Reduced	Absent	Normal	Present
10	24	20/200	20/200	Present	Present	Absent	Atrophic macula OU	Reduced	Absent	Normal	Present
11	10	20/200	20/200	Present	Present	Absent	Normal	Reduced	Absent	Normal	Present
12	23	Hand motion*	20/200	Present	Present	Reduced	Normal	Mildly reduced	Absent	Normal	Absent
13	18	20/70	20/80	Present	Absent	Reduced	Normal	Mildly reduced	Absent	Normal	Absent

Patients 8–11 were unable to score below 500 on the Farnsworth-Munsell 100 hue test and could not do series 8 on the Lanthony test.
*Congenital cataract OD.

Table 4 *Patients with optic neuritis/dominant optic atrophy**

Patient	*Age (yr)*	*Diagnosis*	*Snellen acuity*		*Visual fields*	*Colour vision*
			OD	*OS*		
14	27	Optic neuritis OU, multiple sclerosis	Hand motion	20/15	Central scotoma OD	Reduced
15	30	Optic neuritis OU, multiple sclerosis	20/60	20/400	Central scotoma OU	Reduced
16	15	Dominant optic atrophy‡	20/25	20/125	Normal	Reduced, no tritan axis

*Only those patients who showed pupillary constriction to darkness.
†Visual evoked potential.
‡Positive family history; normal computed tomography studies.

less than one second. The pupillary constriction in this patient was small and best seen with the infrared television apparatus. Two patients (Nos 12, 13) with the less severe form of achromatopsia, incomplete achromatopsia,[3] did not constrict their pupils prior to dilatation and showed pupillary responses that were indistinguishable from normals.

Patients with optic nerve disease. Two patients with bilateral optic neuritis and one patient with dominant optic atrophy were found to show pupillary constriction to darkness (Table 4, Fig. 6). The mean latency of the response was 280 ms. The average amplitude of constriction was 0·7 mm and mean duration 1·4 s. All three patients had normal electroretinograms and dark adaptation thresholds. The amplitude and the duration of constriction were less in the patients with optic nerve disease than in the patients with retinal disease. Twenty-one other patients with optic neuritis and seven other patients with dominant optic atrophy were also evaluated with our infrared apparatus, but showed no constriction to darkness. When patients with optic neuritis who showed constriction and those who did not were compared, there was no difference in visual acuity, visual fields, colour vision, or visual evoked potential.

Pearl mutant mice.[7] Six Pearl mice were examined with infrared pupillometry. Their pupils promptly dilated to darkness. There was no initial pupillary constriction.

Discussion

Characteristics of the phenomenon. In the patients who showed the phenomenon the pupillary constriction was very much as described by Barricks *et al.* and Flynn *et al.*[1 2] It occurred every time the lights were turned out, yet the pupillary reactions of these patients were otherwise normal. The latency of the abnormal transient constriction (time from lights out to the beginning of the constriction) was similar to the latency of the normal pupillary dilatation in darkness.

Prevalence of the phenomenon in patients with retinal disease. The darkness constriction of the pupil was not found in every patient with retinal disease. Five patients, of the nine with congenital stationary night blindness who were examined, did not show the phenomenon. These five could not be separated on the basis of their visual function tests from the four patients who did show a pupillary constriction to darkness.

Only two patients with incomplete achromatopsia were examined, and their pupillary responses to darkness were normal. This raises the possibility that only those patients with complete congenital achromatopsia show the abnormal pupillary response. Patients with retinitis pigmentosa did not show the phenomenon.

Age of the patients with retinal disease. We found that the pupillary constriction to darkness was not confined to the very young. Eight of our patients with retinal dysfunction showed the phenomenon. Four of these were older than 20 and two were over 30. Furthermore three patients with congenital stationary night blindness who did not show pupillary constriction were less than 10 years old.

Clinical value of the observation. In most of our patients with retinal disease we were able to see the pupillary constriction by shining a handlight on the face from below and switching the room lights on and off, while the patient fixed his vision on a distant object. In a young child with nystagmus and poor vision, colour vision cannot be tested, and the clinical sign of pupillary constriction to darkness suggests the diagnosis of hereditary retinal disease and demands the appropriate electrophysiological tests.[2 8] Three patients with bilateral optic nerve disease also showed small initial constrictions to darkness of short duration that were difficult to see without the infrared television equipment. So if the darkness constriction is clinically visible, retinal disease should still be suspected.

Mechanism of the phenomenon. Flynn *et al.*[2] tried to account for the phenomenon in patients with congenital achromatopsia and congenital stationary

Fundus appearance	*VEP*†	*Photopic ERG*	*Flicker ERG*	*Scotopic ERG*	*Pupillary constriction to darkness*
Disc pallor OD	Absent OD Delayed OS	Normal	Normal	Normal	Present
Disc pallor OU	Delayed OU	Normal	Normal	Normal	Present
Temporal disc pallor OU	Not done	Normal	Normal	Normal	Present

night blindness by proposing a transient delay in the rod bleaching signal that would allow the small cone bleaching signal briefly to constrict the pupils as the lights were turned off. Yet Alpern *et al.*[9] found that the rod bleaching signal appeared to be normal in congenital stationary night blindness, but the perception of real light quanta from rods was defective—hence the night blindness. It is difficult to explain a delay in what seems to be an otherwise normal rod bleaching signal. This mechanisms does not explain the phenomenon in optic nerve disease nor does it explain the phenomenon in achromatopsia, a condition in which the cones are defective and rod function appears to be normal.

The phenomenon of pupillary constriction to darkness remains unexplained. Our observation of the phenomenon in an occasional patient with bilateral optic nerve disease only deepens the mystery. The animal model of congenital stationary night blindness that we examined failed to show the phenomenon, so an experimental model of pupillary constriction to darkness has not yet been found.

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References

1 Barricks ME, Flynn JT, Kushner BJ. Paradoxical pupillary responses in congenital stationary night blindness. *Arch Ophthalmol* 1977; **95:** 1800.

2 Flynn JT, Kazarian E, Barricks M. Paradoxical pupil in congenital achromatopsia. *Int Ophthalmol* 1981; **3:** 91-6.

3 Smith VC, Pokorny J. Cone dysfunction syndromes defined by colour vision. In Verriest G. ed. *Colour vision deficiencies V.* Bristol: Adam Hilger, 1980: 69-82.

4 Carr RE. Congenital stationary night blindness. *Trans Am Ophthalmol Soc* 1974; **72:** 448-87.

5 Schubert G, Bornschein H. Beitrag zur Analyse des menschlichen Elektroretinogramms. *Ophthalmologica* 1952; **123:** 396-413.

6 Riggs LA. Electroretinography in cases of night blindness. *Am J Ophthalmol* 1954; **38:** 70-8.

7 Balkema GW, Mangini NJ, Pinto LH. Discrete visual defects in Pearl mutant mice. *Science* 1983; **219:** 1085-7.

8 O'Connor PS, Tredici TJ, Ivan DJ, Mumma JV, Shacklett DE. Achromatopsia: Clinical diagnosis and treatment. *J Clin Neuro-Ophthalmol* 1982; **2:** 219-26.

9 Alpern M, Holland MG, Ohba N. Rhodopsin bleaching signals in essential night blindness. *J Physiol (Lond)* 1972; **225:** 457-76.

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Serum antibody level to S-antigen in children with chronic uveitis

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SUMMARY Bovine S-antigen was purified by gel filtration and ion exchange chromatography according to previously described techniques. An enzyme linked immunosorbent assay (ELISA) using antiserum to bovine S-antigen raised in guinea-pigs was employed to detect S-antigen in the chromatographic fractions. The purity of the S-antigen was determined by SDS-PAGE electrophoresis, where a single band was found. The purified S-antigen in microgram quantities together with Freund's complete adjuvant induced uveitis in rats two weeks after injection into the foot pad. Serum samples from children suffering from chronic uveitis and healthy children were tested for antibodies to S-antigen by the ELISA. A statistically significant difference in the level of specific antibodies between patients and controls was found. There was no clear-cut correlation between the severity of uveitis and antibody titre, but cases with retinal involvement and aggressive uveitis all showed definite elevations of antibodies to S-antigen.

The isolation of a pathogenic antigen, S-antigen, from retina[1 2] of various species, and the demonstration of uveitis in monkeys immunised with this antigen, implicate the retina as the source of a uveitogenic autoantigen.[3] Elevated titres of antibody to S-antigen have been reported in patients with uveitis[4] as well as cellular immune responses.[5] These findings suggest that retinal S-antigen may be a causative or contributing factor in human uveitis.

Chronic iridocyclitis, which may be associated with rheumatoid arthritis, is a particularly destructive disease in children, and the prognosis for vision is often uniformly bad.[6–11] Since young tissues respond to noxious stimuli more vigorously and extensively than old ones, the changes in immunological parameters may be easily observed in children.[11] The purpose of this study was to investigate antibody titres to retinal S-antigen in children suffering from chronic uveitis. We report elevated antibody titres to S-antigen in these children.

Materials and methods

Patients. The antibody titres reported here are based on blood samples taken from 16 patients suffering from uveitis and on blood samples from 22 normal control individuals. This series of children with chronic uveitis was selected from inpatients admitted to the Department of Paediatric Ophthalmology of the Helsinki University Central Hospital. All children with uveitis had chronic inflammation in one or both eyes that caused visual impairment. The disease was almost always in the active stage (Table 1). The control group consisted of 22 children with no signs of ocular inflammation. These children were admitted to hospital for amblyopic treatment or squint surgery. All the children with uveitis and the control children were examined and followed up by R.J.U. Blood samples were drawn from the patients and the controls at the initial examination. The patients received topical steroid and mydriatic drops. In addition many of them with active disease and ocular hypotony received parabulbar steroids—triamcinolone acetonide (Kenacort-T) 5 mg—once a week on

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Table 1 *Comparison of patients with high and low titres to S-antigen*

	High antibody	*Low antibody*
Average age	10·4 yr	11·1 yr
Average duration	1·5 yr	4·0 yr
Clinically active	8/8 cases	5/8 cases
Binocular uveitis	5/8 cases	5/8 cases
Retinal involvement	5/8 cases	1/8 cases
HLA-B27 positive	3/7 cases	1/4 cases
JRA (Still's disease)	3/8 cases	3/5 cases

several occasions. None of the children received systemic steroids.

Each patient with uveitis had a complete medical, social, and ocular history taken, and a complete eye examination with emphasis on the following parameters: visual acuity, aqueous flare, cells in the aqueous humour and/or in the vitreous, keratic precipitates (KP), band keratopathy, synechiae, oedema in the posterior segment of the eye, and hypotony. In addition all the uveitis patients included in the study were tested for complete blood count, erythrocyte sedimentation rate, serum antistreptococcal, antistaphylococcal, and antinuclear antibodies, rheumatoid factor in serum, HLA antigens, and serologic tests for toxoplasma and yersinia antibodies. Chest, sinus, and orthopantomographic *x*-ray examinations were also performed in all patients to exclude infectious types of uveitis.

Preparation of serum samples. Serum was drawn off 10 ml of clotted blood, centrifuged at low-speed, and stored at −20°C. Before the determination of antibody titres to S-antigen the serum was heat-inactivated (56°C for 30 min). Antiserum to bovine S-antigen raised in guinea-pigs was received from Dr D Gregerson. The preparation of this has been described earlier.[4] Rabbit anti-guinea-pig IgG was purchased from Bionetics, goat anti-rabbit IgG conjugated to alkaline phosphatase from Miles-Yeda, and rabbit anti-human IgG from Boehringer.

Preparation of S-antigen. S-antigen was isolated from bovine retinas by the technique described by Wacker *et al.*[1] with the modifications described below. A 20% (w/v) suspension of bovine retina was prepared in ice-cold phosphate buffer, pH 7·2. The retina homogenate was centrifuged 80 000 *g* at 4°C for 1·5 h, and the clear supernatant containing S-antigen was harvested by aspiration. The antigen was precipitated from harvested supernatant by half-saturated ammonium sulphate and purified by gel filtration on Sephadex G-150 followed by two passes on ion exchange columns (DEAE or QAE G-50). In gel filtration the material was eluted with phosphate buffer, pH 7·2, and in ion exchange chromatography with a linear salt gradient in Tris-Cl buffer at pH 7·9. Protein determinations of aliquots of fractions were done by absorbance spectrophotometry (280 nm), and the presence of S-antigen was determined by the ELISA (see below).

Active fractions were pooled, dialysed, and concentrated. As a final step the antigen was passed through an immunoabsorbent column of anti-bovine serum.[12] This was done to absorb any possible remnant of bovine serum from the S-antigen purified material, which could react with antibodies in human serum at a later stage.

The S-antigen, purified as described above, gave a single band of 50 000 molecular weight in SDS-polyacrylamide gel electrophoresis (SDS-PAGE). To determine the uveitogenic activity of the S-antigen, 50 µg was emulsified in Freund's complete adjuvant and injected into the hind foot pads of albino Sprague Dawley rats.[13] Autoimmune uveitis (EAU) was induced in about two weeks in these animals.

ELISA. The ELISA (enzyme-linked immunosorbent assay) was performed according to Voller *et al.*[14] with the modifications described below.

Screening of chromatographic fractions by ELISA. Each fraction to be tested for S-antigen activity was diluted 1:100 in distilled water and a 10µl aliquot was transferred into the wells of micro-ELISA plates followed by 240 µl of coating buffer (15 mM Na_2CO_3, 35 mM $NaHCO_3$, and 0·02% NaN_3, pH 9·6). The plates were covered and incubated at 22°C for 2h. Phosphate-buffered saline-polysorbate (Tween 20) (PBS-Tween) was used to rinse the wells three times, and 250 µl of guinea-pig antiserum against bovine S-antigen (diluted at 1:1000 in PBS-Tween) was added. After incubation at 37°C for 1 h the plates were rinsed three times with PBS-Tween. Thereafter rabbit anti-guinea-pig IgG (diluted at 1:1000 in PBS-Tween) was added. After incubation at 37°C for 1 h the plates were rinsed three times with PBS-Tween and 250 µl of goat anti-rabbit IgG conjugated to alkaline phosphatase (diluted at 1:1000 in PBS-Tween) was added. After incubation for 1 h at 37°C the wells were rinsed four times with Tris-HCl, pH 7·4, followed by addition of 250 µl of substrate solution (1M Tris base, 1M NaCl, 6 mM p-nitrophenyl phosphate, 2 mM $MgCl_2$ and 0·02% NaN_3, pH 9·0). The plates were incubated at 22°C overnight and read at 410 nm spectrophotometrically.

Determination of human antibody levels to S-antigen. In order to absorb the non-specific anti-bovine activity of human sera, preincubation of the human serum with newborn calf serum, each diluted 1:25 n PBS-Tween also containing 1 mg/ml bovine serum albumin, was carried out overnight. In three controls no preincubation was carried out.

10 µl of the antigen solution containing about 50 ng

of S-antigen was dispensed into the wells of micro-ELISA plates, followed by addition of 240 µl of coating buffer (see above). The plates were covered and incubated at 22° for 2 h. The wells were then rinsed three times with PBS-Tween. Preabsorbed human sera were diluted in PBS-Tween and the diluted serum was added in 250 µl aliquots to the wells. For each dilution a duplicate measurement was performed. The serum samples were diluted 1:25, 1:50, 1:100, 1:200, 1:400, 1:800. However, since the serum was already diluted 1:25 and added to an equal volume of 1:25 diluted calf serum for preincubation, the final dilutions of patient serum tested for S-antibody concentration were 1:50, 1:100, 1:200, 1:400, 1:800, 1:1600. The serum samples were incubated for 1·5 h at 37°C and rinsed with PBS-Tween-BSA three times. Thereafter 250 µl of rabbit anti-human IgG (diluted at 1:50 000 in PBS-Tween-BSA) was added and incubated at 22°C for 1 h. The wells were rinsed three times with PBS-Tween-BSA, and 250 µl of goat anti-rabbit IgG conjugated alkaline phosphatase (diluted at 1:2000 in PBS-Tween containing a 1:400 dilution of calf serum) was added and incubated at 37°C for 1 h. The wells were then thoroughly rinsed with Tris-HCl buffer followed by incubation with substrate and the absorbance was measured spectrophotometrically. For each serum sample there was a duplicate control (diluted 1:50). This consisted of two uncoated (no S-antigen) wells in which all the subsequent incubation steps were performed. A negative control thus showed that S-antigen coating of the well as a prerequisite for reaction. A positive control would have shown non-specific sticking of the antibodies to the plastic surface.

Data analysis. Antibody titration curves were straightened and the greatest dilution showing positive reaction to S-antigen was used. A spectrophotometric reading which was at least twice the reading of the control sample (background) was considered as a positive reaction to S-antigen. A dilution of 1:50 was defined as a titre of 1, 1:100 as a titre of 2, 1:200 as a titre of 3, and so on. Both the two-tailed Student's *t* test and the Wilcoxon's rank sum test (non-parametric) were used to determine whether the response of the patient group differed from that of the normals.

Results

Serum samples obtained from children with chronic uveitis and from healthy individuals were assayed for anti-S activity with the ELISA. The results are presented in Fig. 1. Statistically significant elevation of titres to S-antigen were found in children with uveitis ($p<0·01$) (both with Student's *t* test and Wilcoxon's test). From the data presented in Fig. 1. it can be seen that some patients had higher titres (antibody titre of 3 or more) and others had lower titres (antibody titre of 2 or less). A comparison of these groups is seen in Table 1. In the group with high titres the incidence of retinal involvement was substantial, and the disease of the patients was in every case in an active stage. Clinically it was clear that the most severe cases with chronic uveitis also had high titres to S-antigen. No clear difference between the two groups was seen if HLA-B27 or CRA was positive in the patients.

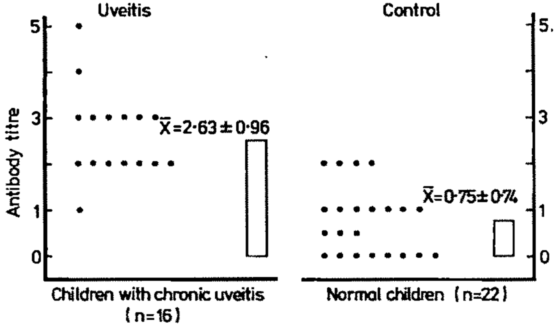

Fig. 1 *Antibody titres of children with uveitis (n=16) and controls (n=22) to S-antigen. At head of each column are arithmetical mean ± standard deviation.*

In normal controls half of the serum samples showed no response at all or a response only in a final dilution of 1:25. Four out of 22 normal control samples showed an antibody response of 1:100 (titre: 2).

Discussion

The retinal soluble antigen (S-antigen) is a uveitogenic organ-specific antigen isolated from the retina of several mammalian species.[16-18] The first report that this soluble antigen was located in the outer segments of photoreceptor cells was by Rahi.[19] We have used previously described techniques to purify this S-antigen from bovine retinas. The S-antigen gave a single band on SDS-PAGE electrophoresis and was pathogenically active in microgram doses. It evoked a form of EAU characterised by abrupt onset of iridocyclitis in rats within two weeks after immunisation, which was followed by development of chorioretinitis. This is in agreement with previous reports[13 20] and confirms the specificity of the antigen used in the present work.

Children with chronic uveitis were selected for the study because it is known that young tissues respond to noxious stimuli more vigorously and extensively than adult ones, and changes in immunological parameters may therefore be easier to study.[11]

Uveitis in children is frequently a more serious disease than in adults.[6-8 21]

By using an indirect enzyme-linked immunosorbent assay the data presented in this report demonstrate that the serum antibody titres in children with uveitis are statistically significantly elevated to bovine S-antigen. This is in agreement with the findings reported by Gregerson *et al.*[4] in adults with uveitis. The human and bovine S-antigens have not yet been sequenced, but there are indications that the S-antigens from these species are very similar both biochemically and immunologically.[22] Although the mean value of the titres was elevated in patients with uveitis (mean antibody titre: 2·63) as compared with the controls (mean antibody titre: 0·75) there were also patients who showed only low antibody titres. In order to find out if the patients with high antibody titres (antibody titres of 3 or more) were different from those with low titres (antibody titres of 2 or less) we compared these groups for several factors described in Table 1. A comparison of the duration of the disease, or binocularity as well as association with HLA-B27 antigen or juvenile rheumatoid arthritis did not reveal significant differences between groups with high and low titres. In the group with high titres, however, the disease of all the patients was in an active stage, and most of them (5 cases out of 8) also had a retinal inflammation. In the group with low titres there was only one case out of eight with retinal inflammation. Clinically it was clear that the children with the most severe form of chronic uveitis all had significantly elevated titres. Not unexpectedly, the children with antibody titres of 4 and 5 had an exceptionally severe form of uveitis in both eyes.

A factor influencing the statistical evaluation was the patient to patient variation in antibody titre. This was also marked in the control group: 8 out of 22 control children showed no antibody titre to S-antigen, but in others it varied from 0·50 to 2. The reason for this is unclear, but it is possible that some of the control sera showed false positive reaction. Non-specific anti-bovine activity which is commonly found in human serum was absorbed by preincubating with calf serum before determination of antibody titre with ELISA. This absorption removes all the anti-bovine serum activity from the human serum.[4] In spite of these precautions it is possible that the purified bovine S-antigen may be cross-reactive with some other unidentified antigen. This non-specific binding and possibly false positive reactions can perhaps be prevented by using human S-antigen together with monoclonal antibodies in an ELISA assay. Such work is now in progress.

We have observed that the antibody titre to S-antigen is elevated in children with uveitis. However, the correlation between the level of activity of the uveitis and the titre to S-antigen is not clear. This is similar to an observation by Rahi *et al.*[23] that antiretinal autoimmunity does exist in sympathetic ophthalmitis though it is not possible to make a definitive diagnosis on immunological grounds alone. To study S-antigens in more detail in the pathogenesis of uveitis would require serial serum samples, so that the antibody level could be correlated with the clinical course of the disease. Abrahams and Gregerson[24] found no longitudinal correlation between clinical activity and anti-S-antigen titres in patients with chronic, recurrent uveitis. However, they found that the titres reached a peak and declined more predictably in those patients who presented with active lesions which subsequently resolved without recurrence. We intend to perform a longitudinal study in children suffering from uveitis with purified human S-antigen together with monoclonal antibodies using an ELISA technique.

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References

1 Wacker WB, Donoso LA, Kalsow CM, Yankeelov JA, Jr, Organisciak DT. Experimental allergic uveitis. Isolation, characterization, and localization of a soluble uveitopathogenic antigen from bovine retina. *J Immunol* 1977; **119:** 1949-58.

2 Dorey C, Tuyen VV, Cozette J, Faure J-P. Isolation and properties of retinal S-antigen. In: Silverstein AM, O'Connor GR, eds. *Immunology and immunopathology of the eye.* New York: Masson, 1979.

3 Nussenblatt RB, Gery I, Kuwabara T, de Monasterio FM, Wacker WB. The role of the retinal S-antigen in primate uveitis. In: Helmsen RJ, Suran A, Gery I, Nussenblatt RB, eds. *Immunology of the eye. Workshop II: Autoimmune phenomena and ocular disorders.* Proceedings of a workshop on autoimmune phenomena and ocular disorders, Dulles Marriott Hotel, Chantilly, Virginia, 2–7 March 1980: 49–65.

4 Gregerson DS, Abrahams IW, Thirkill CE. Serum antibody levels of uveitis patients to bovine retinal antigens. *Invest Ophthalmol Visual Sci* 1981; **21:** 669–80.

5 Nussenblatt RB, Gery I, Ballintine E, Wacker WB. Cellular immune responsiveness of uveitis patients to retinal S-antigen. *Am J Ophthalmol* 1980; **80:** 173–9.

6 Kimura SJ, Hogan MJ. Uveitis in children of 274 cases. *Trans Am Ophthalmol Soc* 1964; **62:** 173–92.

7 Hogan MJ, Kimura SJ, O'Connor GR. Peripheral retinitis and chronic cyclitis in children. *Trans Ophthalmol Soc UK* 1965; **85:** 39–52.

8 Witmer R. *Uveitis in Kindesalter.* Proceedings of the XX International Congress of Ophthalmology, Munich 14–19 August 1966. Amsterdam: Excerpta Medica, Int Congr Ser, No. 146, 1966: 317–25.

9 Giles CL. Anterior uveitis in children. *Arch Ophthalmol* 1963; **70:** 779–85.

10 Sen DK. Endogenous uveitis in Indian children: analysis of 94 cases. *J Pediatr Ophthalmol* 1977; **14:** 25–32.

11 Knox DL. Disorders of the uveal tract. In: Harley RD, ed. *Pediatric ophthalmology*, Part II, 1982: 515–48.

12 Tallberg T, Eskola L, Borgström GH. Immunological studies using insoluble protein polymers. *Proteins of Biological Fluids* 1970; **18:** 415–23.

13 Marak GE, Rao NA. Retinal S-antigen disease in rats. *Ophthalmic Res* 1982; **14:** 29–39.

14 Voller A, Bidwell D, Bartett A. Microplate enzyme immunoassays for the immunodiagnosis of virus infections. In: Rose NR, Friedman H, eds. *Manual of clinical immunology.* Washington DC: American Society for Microbiology, 1976: 506.

15 Wacker WB. Isolation of retinal S-antigen and its role in experimental ocular autoimmunity. In: Sears ML, ed. *New directions in ophthalmic research.* New Haven: Yale University Press, 1981.

16 Wacker WB. Retinal autoimmunity and the pathogenesis of uveitis. In: Helmsen RJ, Suran A, Gery I, Nussenblatt RB, eds. *Immunology of the eye. Workshop II:* Autoimmune phenomena and ocular disorders. Proceedings of a workshop on autoimmune phenomena and ocular disorders, Dulles Marriott Hotel, Chantilly, Virginia, 5–7 March 1980: 11–31.

17 Dorey C, Cozette J, Faure J-P. A simple and rapid method for isolation of retinal S-antigen. *Ophthalmic Res* 1982; **14:** 249–55.

18 Tuyen VV, Faure J-P, Thillaye B, de Kozak Y, Fortier B. Antibody determination by ELISA in rats with retinal S-antigen-induced uveoretinitis. *Curr Eye Res* 1982–3; **2:** 7–12.

19 Rahi AHS. Autoimmunity and the retina. I. Antigenic specificity of photoreceptor cells. *Br J Ophthalmol* 1970; **54:** 441–4.

20 De Kozak Y, Thillaye B, Renard G, Faure J-P. Hyperacute form of experimental autoimmune uveito-retinitis in Lewis rats; electron microscopic study. *Albrecht von Graefes Arch Klin Ophthalmol* 1978; **208:** 135–42.

21 Giles CL, Schlaege TF. Childhood uveitis. *Int Ophthalmol Clin* 1977; **17:** 75–85.

22 Dorey C, Mirshahi M, Brandao E, de Kozak Y, Faure J-P. Properties of human retinal S-antigen. *Ophthalmic Res* in press.

23 Rahi A, Morgan G, Levy I, Dinning W. Immunological investigations in post-traumatic granulomatous and non-granulomatous uveitis. *Br J Ophthalmol* 1978; **62:** 722–8.

24 Abrahams IW, Gregerson DS. Longitudinal study of serum antibody responses to bovine retinal S-antigen in endogenous granulomatous uveitis. *Br J Ophthalmol* 1983; **67:** 681–4.

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Penetration of timolol eye drops into human aqueous humour: the first hour

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SUMMARY Samples of aqueous humour were removed from 26 eyes at the start of cataract extraction. Two drops of timolol 0·5% had been instilled into the conjunctival sac 12–71 minutes before operation. Analysis by gas chromatography showed a mean timolol concentration of 55·46 ng/mg, with a range of 8 to 100 ng/mg.

In a previous paper[1] we reported concentrations of timolol in human aqueous humour after the first hour following instillation into the conjunctival sac of 2 drops of timolol eye drops 0·5% (500 μg per 100 mg): these ranged from 150 ng per 100 mg between the first and second hours to 10 ng per 100 mg towards the end of 7 hours, that is, there seemed to be a progressive fall from the time of initial observations. Aqueous samples were taken in the preliminary stages of cataract extraction. These data provided no information about concentrations during the first hour following instillation of the eye drops, an omission made good in the present series.

Previous studies have been done in albino rabbits either by measuring total radioactivity after instillation of labelled drugs[2–5] or by assaying β blockers by gas chromatography.[2–6] Aqueous levels after instillation of timolol were higher than those achieved after atenolol or metoprolol,[4] whereas propranolol, practolol, oxprenolol, and alprenolol gave higher aqueous humour levels than timolol.[6]

Patients and methods

Two drops of timolol 0·5% were instilled into the conjunctival sacs of 30 patients 12–71 minutes before removal of samples of aqueous humour at cataract extraction. In three cases the volume was too small to allow analyses, while in one case the time interval was not clearly enough recorded; accordingly these were discarded, to leave 26 valid observations.

At the beginning of the operation of cataract extraction a conjunctival flap was made, then a limbal groove. In some patients a tuberculin needle was used to perforate the deepest layers of the corneoscleral junction to aspirate aqueous, while in others the incision was deepened into the anterior chamber for 1–2 mm at 12 o'clock to allow entry of the blunt tip of a Rycroft cannula. Each sample was stored in a small stoppered plastic tube at −80°C or in dry ice during transport.

Most patients had general anaesthesia (halothane) preceded by diazepam (Valium) 10 mg. Some had local, including retrobulbar, anaesthesia. All had phenylephrine 10% eye drops preoperatively, and some had atropine 1% eye drops 24 hours and 1–2 hours before operation.

CHEMICAL ANALYSIS

A modification of the procedure of Tocco *et al.*[7] was employed for the assay of timolol. The method is based on the gas chromatographic electron-capture determination of the heptafluorobutyric ester derivative of timolol with desmethyltimolol as internal standard. The chromatograph used was a model 5730 (Hewlett-Packard) equipped with a ^{63}Ni electron capture detector. A 1·1 m×3 mm glass column packed with 3% OV17 on Gaschrom Q (100–120 mesh) was employed with a carrier gas of argon/methane (90:10) at a flow rate of 55 ml/minute. Temperature programming was carried out by maintaining the oven at 195° C for 10 minutes followed by increasing 4°/minute up to 260° and then heating at 260° for a further 4 minutes. The retention times for timolol and its internal standard were 7·1 and 8·6 minutes respectively.

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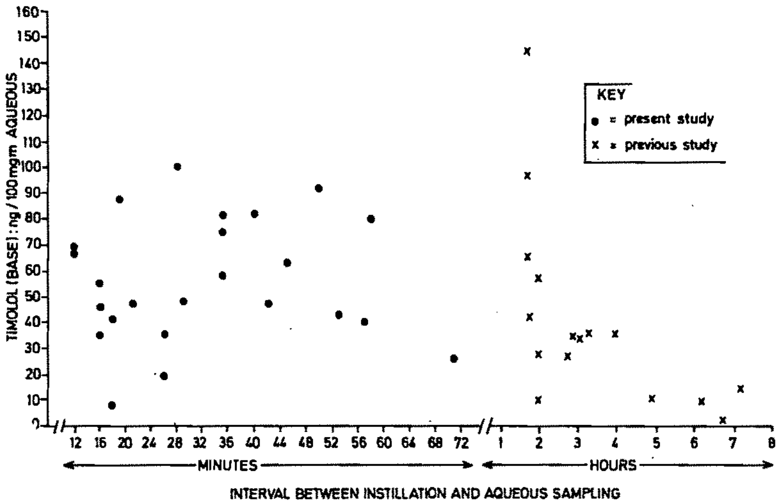

Fig. 1 *Results of instillation of timolol drops.*

Results

See Fig. 1, which includes results from our previous study. Within 71 minutes from instillation of drops the concentration of timolol ranged from 8 to 100 ng per 100 mg of aqueous, mean 55·46 ng.

The results suggest that an individual eye usually achieves a peak concentration within the first 60–70 minutes following instillation of drops, but there seems to be no particularly consistent point of time when that occurs. Actually the highest peak concentration, both series being considered together, was 145 ng at just under 2 hours after instillation.

Discussion

Previous studies in rabbits with ^{14}C-labelled blockers showed that, after instillation of a 0·5% solution of timolol, the peak total radioactivity was equivalent to 300–600 ng per 100 mg and occurred at an interval of 30–60 minutes.[2-4] That concentration is around 6–10 times higher than the human values we have found, perhaps mainly owing to the thicker human corneoscleral envelope and in spite of the lower turnover of aqueous humour in elderly cataract patients compared with that in rabbits.

The variance of our observations is not particularly large, but artefacts may account for some of it, such as some dilution of aqueous by serum during the process of aspiration. Similarly, the preliminary manipulations of the eye and the anaesthetic used may affect the observations. The analytic chemical technique can be expected to contribute a little to the variance. Residual 'intrinsic' variance can be attributed to differences between patients in tear flow, corneal permeability, tissue uptake, clearance by blood flow in conjunctival and intraocular blood vessels, outflow of aqueous humour, and rate of movement of drug into the lens and vitreous. More general factors are the general state, and especially the age, of the patient as indicators of the rate of metabolism.

This method of using patients having intraocular operations for an unrelated condition provides a useful and probably the only acceptable means of collecting data on drug penetration into the aqueous humour in man as opposed to animals. Although we have not observed any deleterious effect from the aspiration procedure it might be that corneal endothelial function might be more compromised than if the aspiration procedure were omitted: no eye was used if insertion of an intraocular lens was planned.

References

1 Phillips CI, Bartholomew RS, Kazi G, Schmitt CJ, Vogel R. Penetration of timolol eye drops into human aqueous humour. *Br J Ophthalmol* 1981; **65:** 593–5.
2 Merck Sharp and Dohme Research Laboratories, USA, and MSD Chibret Research Institute, France. Timolol maleate ophthalmic solutions: preclinical evaluation. 9 January 1978.
3 Ros FE, Innemee HC, Van Zwieten PA. Penetration of atenolol in the rabbit eye. *Albrecht von Graefes Arch Klin Ophthalmol* 1978; **208:** 235–40.
4 Ros FE, Innemee HC, Van Zwieten PA. Ocular penetration of β-adrenergic blocking agents. An experimental study with atenolol, metoprolol, timolol and propranolol. *Doc Ophthalmol* 1979; **48:** 291–301.
5 Schmitt CJ, Lotti VJ, Le Douarec JC. Penetration of timolol into the rabbit eye. Measurements after ocular instillation and intravenous injection. *Arch Ophthalmol* 1980; **98:** 547–51.
6 Schmitt CJ, Lotti VJ, Le Douarec JC. Penetration of five beta-adrenergic antagonists into the rabbit eye after ocular instillation. *Albrecht von Graefes Arch Klin Ophthalmol* 1981; **217:** 167–74.
7 Tocco DJ, De Luna FA, Duncan AEW. Electron capture determination of timolol in human plasma and urine. *J Pharm Sci* 1975; **64:** 1879–81.

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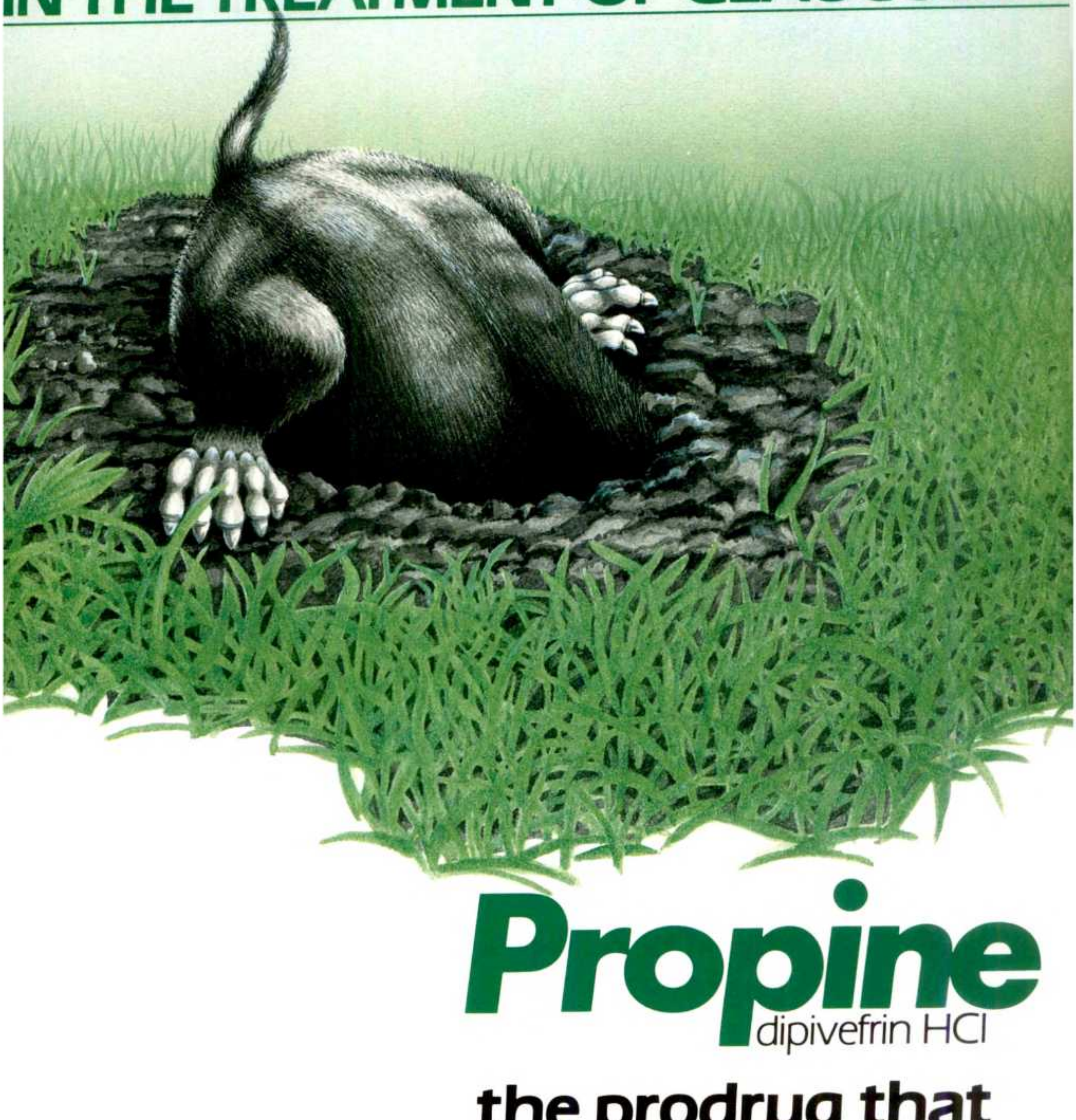

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Possible cataractogenic effect of radionuclides deposited within the eye from the blood stream

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SUMMARY The clinical and histological examination of a cataract in a man of 47 is described together with a review of the deposition of radionuclides in the eye. It is suggested that the cataract was possibly due, at least in part, to irradiation of the sensitive cells in the germinative zone of the lens epithelium by alpha particles deposited in the pigmented tissues of the eye from the ^{239}Pu circulating in the blood.

It has long been recognised that exposure to external ionising radiation may result in a posterior polar cataract in rats,[1] rabbits,[2] and man,[3] the primary injury being to the cells in the germinative zone of the lens epithelium. This is a single layer of cells under the capsule on the anterior face of the lens only. The cells of the germinative zone continue to divide throughout life (at an ever decreasing rate), and the daughter cells gradually differentiate into lens fibres which make up the body of the lens.

Ionising radiation permanently damages the cell nucleus in such a way that the products of cell division are abnormal and do not form normal lens fibres. The cell debris and abnormal fibres, resulting from division of the irradiated cells, gradually move from the equator to the posterior pole of the lens, where they form a disorganised plaque of material opaque to light. The higher rate of cell division in the young lens correlates with its greater sensitivity to radiation.[4 5] Some of the peculiarities of radiation cataract arise from the fact that new lens fibres are laid down throughout life by slow proliferation of epithelium, so that, since no phagocytic system exists (the lens is enclosed in a capsule which is impermeable to cells), a damaged epithelial cell contributes permanent damage to the lens in the form of a damaged fibre. With the continuous growth with age, the damaged cells and fibres get 'pushed' under the capsule to the posterior pole of the lens and form a posterior polar cataract. Further opacities may later develop throughout the lens, and the condition then cannot clinically be distinguished from a senile cataract.

Little consideration, however, has been given to the possible cataractogenic effects of radionuclides deposited within the eye from the blood stream, though it is known that such deposition may occur. Stover *et al.*[6] reported that there was prolonged retention of ^{239}Pu, an alpha particle emitter, in the eyes of beagles after intravenous injection. Four years after the injection the concentration in the eye as a whole was a little over 10 times that in serum. When the ^{239}Pu was estimated in the separate parts of the eyes of dogs it could not be detected in cornea, lens, or vitreous body but was highest in iris and choroid, the pigmented parts.[7] The eyes of dogs cannot, however, be directly compared to the human eye since part of the choroid is replaced by a tapetum lucidum—a structure not found in man.

Non-radioactive barium and strontium are normally present in the choroid and iris of cattle, pigmented rabbits, and, in lower concentrations, in man.[8] ^{226}Ra, ^{228}Th, and ^{210}Po have been found in the choroid and iris of cattle. The concentration of ^{226}Ra noted was comparable with that in bone.[9] Radioactive strontium, ^{90}Sr, also concentrated in iris, ciliary body, and choroid of the pigmented rabbit eye, and there was only a slow release from these tissues.[10] ^{90}Y, on the other hand, a decay product of ^{90}Sr, was not found to be concentrated in pigmented areas of the rabbit's eye like ^{90}Sr but in the retina.

Further, Holtzman and Sha[11] measured the radium and calcium content in the eyes of two persons with a known high body burden of ^{226}RA. They found the greatest concentration of ^{226}Ra was in the sclera, iris, and choroid and similarities between the Ra/Ca ratio in the human choroid and that in bone (whole body).

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They suggest this may indicate that the dose rate to the choroid may be similar to that of bone. This is clearly wrong. The calcium concentration in the bone is very much larger than in the choroid, so that, with the radium and calcium ratio the same, the concentration of radium in the bone and therefore the dose is much larger in bone than in the choroid.

The importance of this uneven distribution of radionuclides within the eye, as far as cataractogenesis is concerned, is that the iris and ciliary body lie adjacent to that area of the lens epithelium in which the radiosensitive cells, capable of division, are situated. These cells are the forerunners of the lens fibres, but after irradiation the daughter cells degenerate before fibre formation begins, and it is these degenerate cells and ill-formed fibres that are the histological counterpart of the radiation cataract at the posterior pole of the lens.

We report here the appearance of a cataract removed from the eye of a relatively young man of 47, which, we suggest, may have been caused, at least in part, by internal radiation from radionuclides deposited in the pigmented tissues of the eye.

Case report

Mr A at the age of 23 started work in June 1950 at an establishment where he might be exposed to ionising radiation. In 1971 it was recorded that his vision was becoming impaired, but he worked there until October 1974, when he was withdrawn on account of his poor eyesight. He was at first an *x*-ray operator, a post which he held (and in which he would be subject to *x*-ray photon irradiation) for about a year until 1951, when he became a process worker in the technical department until 1974. During this period he was potentially subject to all the radiation hazards associated with the type of work involved, namely, plutonium ingestion, external exposure to beta and gamma rays and fast neutrons, and inhalation of plutonium and other alpha and beta emitting radionuclides.

Up to 1970 the practice of the establishment was to assume that eye doses were the same as the whole body doses, which were measured by a film badge worn at chest level. In 1971 lead-loaded rubber aprons were introduced to provide extra whole body protection in certain work where it was not possible to provide adequate shielding in the 'glove boxes.' The chest level film badge was worn under the apron to record the whole body dose, and it was thought that the eye dose could be assessed by multiplying the whole dose by a calculated factor. Measurements, however, showed that this approach was not satisfactory (it overestimated the eye dose, and the factor differed with type and place of work). Therefore late in 1973 workers were issued with 'cap badges' to be worn at forehead level, from which to infer eye doses. Some details of his radiation dose are shown in Table 1.

Table 1 *Mr A: Occupational radiation doses*

Time period, years	*Duration*	*Whole body dose, rems*	*Neutron dose,* rems*	*Eye lens dose, rems**
1950–59	10	18·40	—	18·40
1960–70	11	36·50	(0·73)	36·52
1971–74	4	11·61	0·45	15·09 or 31·99
Total		67		70 or 87†

*Included in whole body dose.
†Depending on method of calculation.

The total whole body dose received by Mr A was 67 rems (an overall average dose of 2·8 rems per year, with values between 4 and 6 rems per year in the period 1967–71 inclusive. His total estimated eye dose was 70–87 rem (annual rate 3–5 rems). It is impossible to calculate his exact cataractogenic dose. The first reports of cataracts in bomb survivors who had received a single large dose of external radiation were made in 1949, about four years after the explosion of the bombs on Japan.[12]

Between 1970 and 1974 Mr A was involved in three known incidents involving contamination of his face with plutonium. In four other incidents his hands or his hands and face were recorded as exposed to alpha irradiation. In all cases the contamination was reported as small and removed within 24 hours by

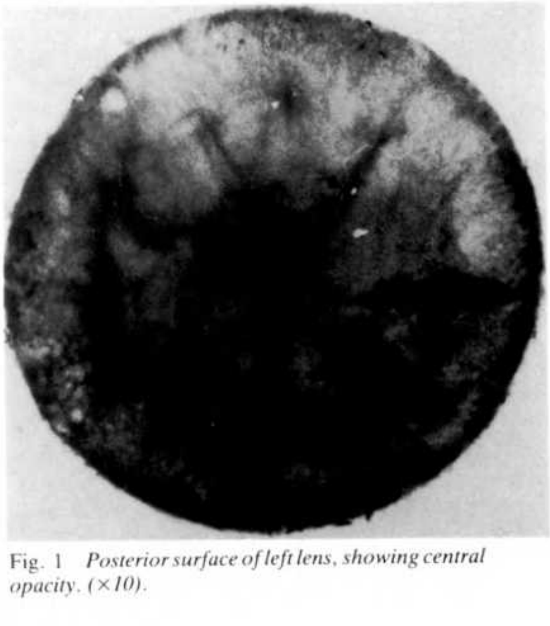

Fig. 1 *Posterior surface of left lens, showing central opacity. (×10).*

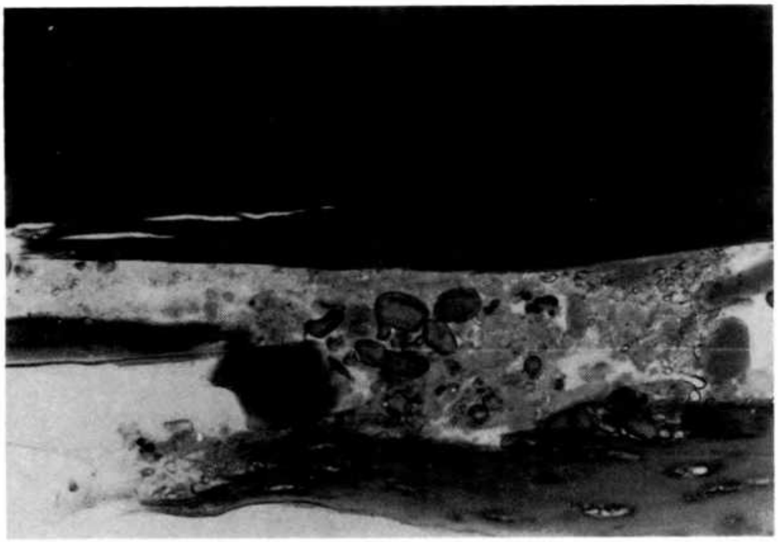

Fig. 2 *Histological section of the posterior polar area of left lens. (H and E, ×230).*

simple procedures. From these incidents, and from his general work, some plutonium must, however, have reached the blood stream, since in 1974 the best estimate of his current plutonium burden was 2 nCi, estimated from urinary excretion. It is recognised that such urinary excretion methods are far from satisfactory for a variety of reasons.[13 14] They can give only an approximate indication of the body burden and in practice usually overestimate this. Measurement in the whole body monitor for ^{239}Pu in the lung was negative. He had never used a microwave oven at home and had not worked in a radar environment.

On account of his poor eyesight Mr A was referred to one of us (TPG), who reported on 23 January 1975: 'The left eye shows some subcapsular lens opacities more marked in the region of the posterior pole; a polychromatic lustre was noted in one small area of these posterior pole opacities. There were also a few opacities near the anterior pole of the lens with the appearance also of one small vacuole. It is possible that Mr A's cataracts may have been due to radiation. The appearance at the moment is not quite typical although it is noted that there is no report of any family history of premature cataract in the family, it is also noted that Mr A is relatively young to be normally expected to develop cataract.'

After removal of the left lens TPG reported on 20 September 1976: 'the "sunflower" appearance of the cataract suggested that this was a complicated cataract with some toxic process being involved. I know of no specific evidence for the type of left lens opacity (or cataract) present being due to radiation.'

In 1977 a cancer (transitional cell type) of the pelvis of the left kidney was removed.

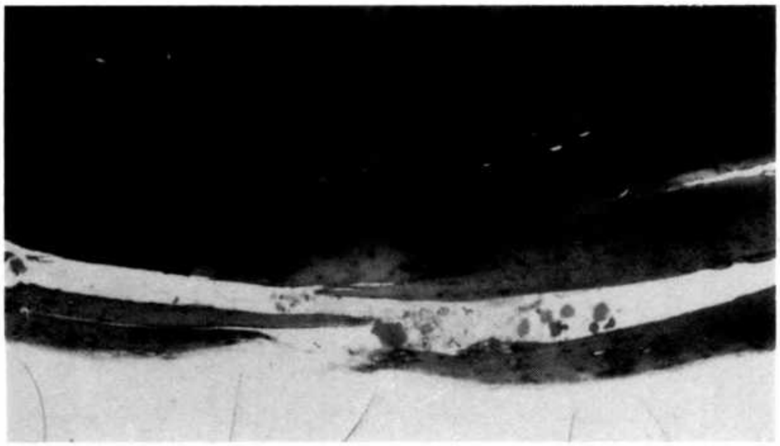

Fig. 3 *Histological section of the posterior polar area of left lens. (H and E, ×57).*

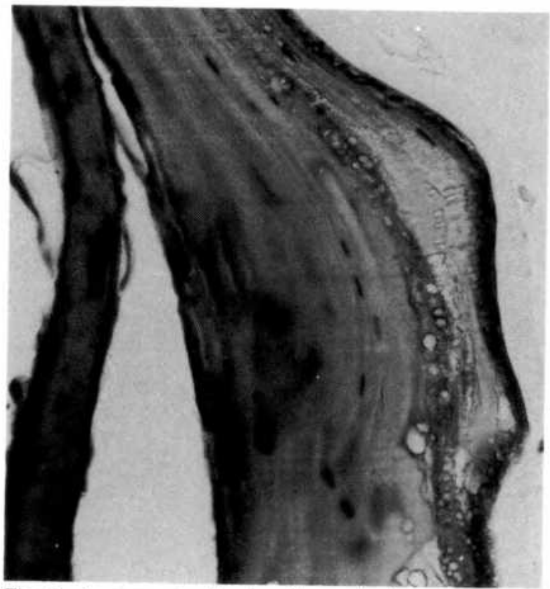

Fig. 4 *Lens equator showing disorganised cortex. (×210).*

HISTOLOGICAL EXAMINATION OF THE CATARACT

Naked eye examination of the extracted lens, fixed in formalin, showed diffuse opacities in the anterior cortex and an opacity at the posterior pole of the lens just under the capsule, together with striate opacities radiating from this into the deeper posterior cortex of the lens Fig. 1. Sections of the lens were made and stained with haematoxylin and eosin. The human cataractous lens is a notoriously difficult material, being liable to fracture during sectioning. Mr A's lens was no exception, and the posterior capsule of the lens detached during the process. Fig. 2 is a photomicrograph of the posterior pole area of the lens taken at high magnification. Fig. 3 is a photomicrograph at a lower magnification which includes the same area as Fig. 2. Disorganisation of cortical lens fibres stretched from the posterior to the equator and anterior pole (Figs. 4 and 5). The deeper posterior cortex was also involved, giving rise to the striate opacities seen in the whole lens before sectioning (Fig. 1). Part of the disorganisation in the anterior cortex may have been due to trauma during cryo-extraction of the lens at operation.

The epithelium, viewed in section, showed gaps between epithelial cells and in other places vacuoles or reduplication of the normal single layer of epithelium (Fig. 6); some cells had pyknotic nuclei (Fig. 7). The sections we have examined did not show any dividing cells, normal or abnormal, nor the spindle shaped cells described by Hayes and Fisher.[15]

Discussion

We have described the appearance during life and the subsequent histological examination of a cataract affecting primarily the posterior pole of the lens of a man of 47, which had some of the characteristics of cataracts induced by external radiation.[3] Mr A's cataract started in the posterior polar region. This parallels the development of cataracts in the populations of Hiroshima and Nagasaki that have been accepted as due to external radiation.[16] Extraction of a posterior polar cataract, or of a senile cataract, is extremely rare below the age of 50.[17] Studies in an Oxfordshire population of 17 695 men aged 40–49 yr over a six-year period found only seven posterior

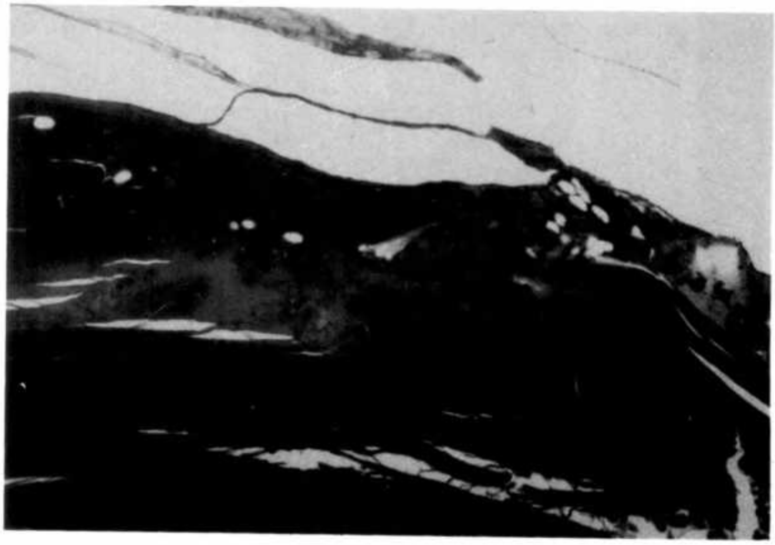

Fig. 5 *Anterior polar area of lens: cortical fibres disorganised and epithelium detached.*

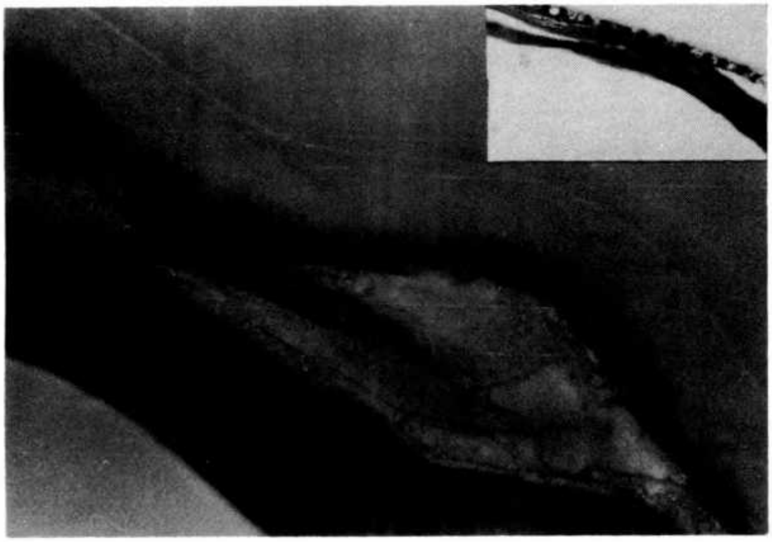

Fig. 6 *Disorganised cortex adjacent to anterior pole showing abnormal epithelium.*

polar subcapsular cataracts, and three senile cataracts needed extraction during that time—that is, 0·66/10 000/yr of posterior polar subcapsular and 0·28/10 000/yr of senile cataracts.

Hayes and Fisher[15] have described posterior polar cataracts extracted from a man who had been exposed for 11 y to low dosage *x* rays. The lenses were removed 26 yr later at the age of 65 yr (personal communication). In most respects the histological and clinical appearance of this lens corresponded with that of Mr A, though feathery fibres were not noted in Mr A's lens, perhaps due to differences in fixation and staining methods. Extraction of Mr A's lens was needed a year and nine months after the posterior polar opacity was first seen clinically, and by that time further changes had taken place, as they had in the lens described by Hayes and Fisher.[15]

A posterior polar subcapsular cataract may occur with the more common features of senile cataract in older age groups. In some patients there may be a recognised cause—for example, trauma or local ocular disease such as retinitis pigmentosa, gyrate atrophy, or uveitis. Other known causes are dystrophia myotonica, systemic steroids, radiation, anorexia nervosa, retinal detachment, absolute glaucoma, intraocular tumours, cyclitis, and iridocyclitis. It must also be recognised that it may be impossible to assign a known cause to a particular

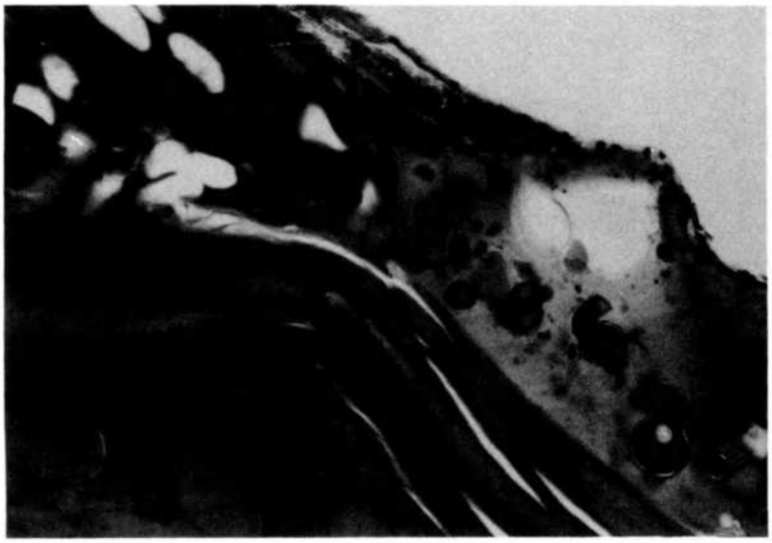

Fig. 7 *Epithelium, showing gaps, vacuoles, and reduplication. (×210).*

posterior polar cataract. If radiation is excluded, Mr A's cataract would be in this class, as he did not suffer from any of the above diseases.

In considering the possible aetiology of the present cataract it should be noted that it occurred in a man of 47 years. The extraction of a posterior polar cataract is extremely rare in a middle aged man.[17] The classic senile cataract occurs in older age groups. In any other person than Mr A the cataract would have been regarded as the unique cataract, originating at the posterior pole, to be found in a large population of the middle aged, but in view of his exposure to radiation the origin of his cataract at least merits discussion.

Mr A had been exposed to low levels of external irradiation but was also known to have a small body burden of ^{239}Pu. It is possible therefore that the sensitive cells of the lens may have been irriadiated also by alpha rays from plutonium deposited from the blood stream in the pigmented epithelium of the iris and ciliary body, which are adjacent to the radiation sensitive cells in the germinative zone of the lens epithelium.

Basing their conclusions on available clinical evidence the International Commission on Radiological Protection[18 19] have recommended that cataract should be regarded as a form of injury, with a dose threshold above 30 rem per year for a life time, and that the occupational dose limits for external radiation of the lens should be 0·3 Sv (30 rems) a year. Cataract is regarded by the ICRP as a 'non-stochastic' effect, that is, its severity varies with the dose, and a threshold dose is therefore to be expected. The latest dose, using the 'best' model in the statistical sense, for lenticular opacities among atom bomb survivors is 110–147 rads for gamma rays. The question whether there is a threshold for neutrons remains uncertain.[16]

The total external radiation dose recorded as received by Mr A over 24 years was equivalent to about two years' exposure at the dose limit for the eye and thus well below the threshold for the occurrence of external radiation-induced cataract. Again the small body burden of plutonium, (2 nCi) as estimated from urine examination, was well below the occupational dose for the whole body. It is however known that ^{239}Pu retention in the human eye exceeds that in many other soft tissues.[20] Autoradiographic studies

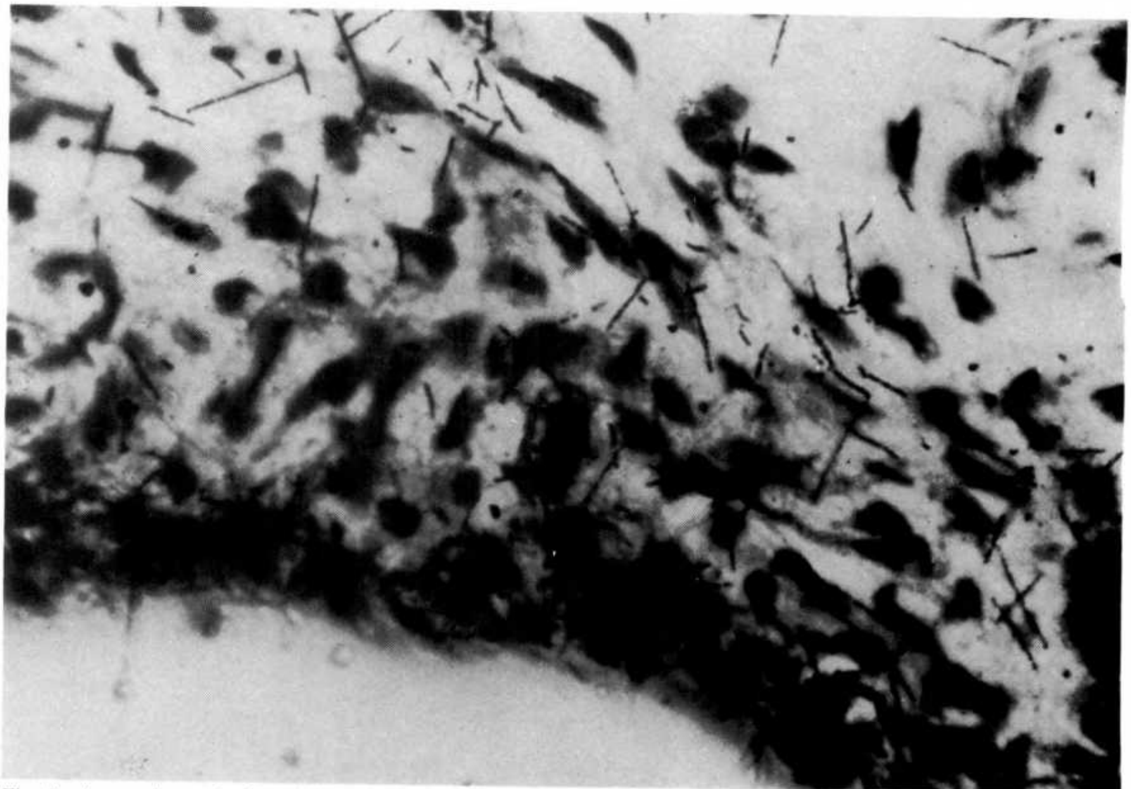

Fig. 8 *Autoradiograph of iris of dog injected intravenously (5 μg/kg) plutonium citrate and killed 24 h later. Note alpha tracks. (×2630).*

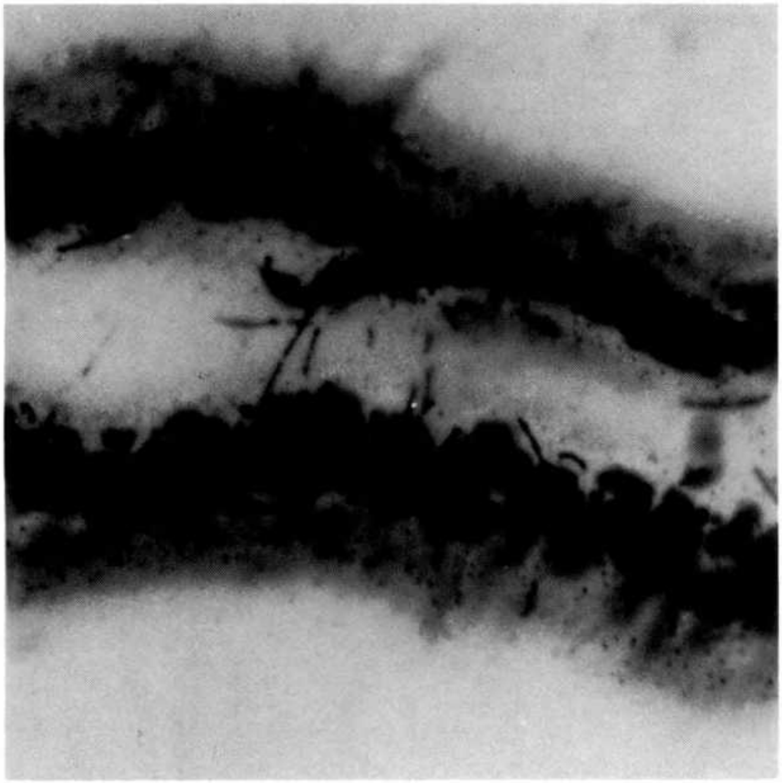

Fig. 9 *Autoradiograph of ciliary process of dog injected intravenously (5 μc/kg) plutonium citrate and killed 24 h later. Note alpha tracks. (×2718).*

of ^{239}Pu distribution in the eye of the dog have shown that this retention in the eye occurs specifically in the iris and ciliary processes (Pirie A, Vaughan J, personal communication) as does that of other radionuclides already discussed. This is shown in Figs. 8 and 9. Some at least of the alpha radiation would be within reach of the radiation sensitive cells in the germinative zone of the lens epithelium, since the range of an alpha particle of plutonium is about 35 μm in tissue,[21] and the distance between the iris and the sensitive cells lies within the same range.[22] Such local irradiation by alpha particles would be expected to be more effective than external penetrating radiation, since alpha particles have a greater biological effect than either gamma rays or neutrons as recognised by the quality factor used in calculating absorbed dose for different types of radiation. The quality factor for alpha particles is 20 compared with 1 for gamma rays and 10 for neutrons.[18] In an early series of observations on a small number of young rabbits Von Sallman and his colleagues found alpha particles to be more cataractogenic than x rays or gamma radiation dose for dose.[22]

Although there are no reports of cataract due to ingested or inhaled plutonium in man or in experimental animals, there is some evidence that cataract is a possible hazard from the therapeutic use of, or industrial exposure to, radium isotopes.

A high incidence of cataract and conspicuous multiple naevi of the iris was first reported in a group of patients given therapeutic amounts of ^{224}Ra in childhood for the treatment of tuberculosis and ankylosing spondylitis.[23] ^{224}Ra decays rapidly to a series of radioactive daughter products which may irradiate soft tissues.[24] It was first given as a mixture known as 'Peteosthor,' which contains platinum and eosin.[23 24] Recent experiments with mice have shown that the tissue distribution of ^{224}Ra was not affected by whether it was given pure or with platinum, but since no cataracts were reported in either set of mice it is not yet known whether platinum can cause cataracts.[25] In the most recent follow-up of 218 juveniles (aged 1–20) and 680 adults (aged 35–47) who received repeated injections of ^{224}Ra about 30 years ago, some in the form of Peteosthor (Spiess H, Mays CW, personal communication), 11 cataracts in juveniles and 25 in adults were found. The average age at which cataract was reported in the juveniles was 35 years, with a range of 14–46 years.[24] The incidence of reported cataracts increased significantly with dosage. In juveniles receiving more than 14·3 μCi/kg ^{224}Ra the cataract incidence was 11/154, while no cataracts were seen among the 57 juveniles receiving lower amounts. In the adult patients whose dose exceeded 14·3 μCi/kg the cataract incidence was 17/245 compared with 7/400 at lower dosage (Spiess H, Mays CW, personal communication). The most recent report on a further group of 274 adults treated with much smaller doses of ^{224}Ra (280 μCi) for ankylosing spondylitis notes seven cases of cataract. The mean time from initiation of treatment was 26 years and the mean age at diagnosis was 66 years. The authors consider that the cataract incidence was not unusual for the age group.[26] The soft tissue dose is not known, but the skeletal dose was several 100 rads in the Spiess juvenile cases[24] compared with 14–125 rads in the adult cases discussed by Wick and Goessner.[26] The character of the cataract is not known in any of the patients treated with ^{224}Ra. However, the high incidence of cataracts in juveniles, some of them as young as 2 years when first treated (Spiess H, Mays CW, personal communication), suggests that the radionuclide ^{224}Ra (or the eosin or platinum) may be cataractogenic, particularly in an age group when the lens is most radiosensitive and high doses are given. The sensitivity of the lens in young animals has been well demonstrated experimentally.[4]

Many women have been exposed to ^{226}Ra and ^{228}Ra through their work as painters of the luminous dials of watches. Löscher[27] reported bilateral posterior subcapsular cataracts in a 56-year-old woman who had worked for 25 years painting luminous radium dials and concluded that these were due to her occupational exposure to radium, which would have included external exposure to gamma rays.[28] More recently Adams *et al.*[28] have surveyed 813 women who were exposed as dial painters before 1930 at a mean age of about 19 years. There were 119 cataracts of unspecified type. The time between first exposure and diagnosis of cataract was less in those whose calculated radium intake to the blood was greater than 50 μCi (140 women) than in those whose intake was lower than this (673 women). The authors conclude that more work is needed before deciding whether or not the cataracts were due to radiation. Though they suggest that duration of employment may be used as an index of the possible participation of external radiation sources in the working environment, they do not discuss whether the radiation involved in cataract induction was alpha particle radiation from ^{226}Ra deposited in the pigmented tissues of the eye or gamma radiation from exposure to environmental sources as is proposed in the case of excess breast cancers in British luminisers.[29]

No excess of cataracts is reported in a large group of patients (approximately 3900) given thorotrast,[30] a contrast medium containing ^{232}Th. The decay chain of ^{232}Th contains both ^{226}Ra and ^{224}Ra.

We are grateful to Dr W J Meredith for estimates of the external radiation dose received by Mr A and to Dr Robin Mole and Mr A Bron for helpful discussions. We thank Mrs Overall for making the autoradiographs and Mr Ian Robertson, Newcastle upon Tyne, for bringing this case to our attention.

References

1 Goldman NH, Liechti A. Experimentelle Untersuchungen über die Genese der Rontgenstars. *Albrecht von Graefes Arch Klin Ophthalmol* 1938; **138:** 722–36.
2 Poppe E. *Experimental investigation of the effect of roentgen rays on the eye.* General Department Norwegian Radium Hospital, Oslo: Kommisjon Hospital, Jacob Dybwad: 1942.
3 Cogan DG, Donaldson DD, Reese AB. Clinical and pathological characteristics of radiation cataract. *Arch Ophthalmol* 1952; **47:** 55–70.
4 Cogan DG, Donaldson DD. Experimental radiation cataracts I. Cataracts in the rabbit following single *x*-ray exposure. *Arch Ophthalmol* 1951; **45:** 508–22.
5 Von Sallmann L. Experimental studies on early lens changes after roentgen irradiation. III. Effect of *x* radiation on mitotic activity and nuclear fragmentation of lens epithelium in normal and cysteine treated rabbits. *Arch Ophthalmol* 1952; **47:** 305–20.
6 Stover BJ, Atherton DR, Mays CW. Studies of the retention and distribution of ^{226}Ra, ^{239}Pu, ^{228}Ra, ^{228}Th, and ^{90}Sz in adult beagles. In: Dougherty TF, Jee WSS, Mays CW, Stover BJ, eds. *Some aspects of internal irradiation.* Oxford: Pergamon Press, 1962: 7–25.
7 Taylor GN, Rehfeld CE, Schneebeli G, Johnson HA. In: Dougherty TF, Jee WSS, Mays CW, Stover BJ, eds. *Some aspects of internal irradiation.* Oxford: Pergamon Press, 1962: 163–78.
8 Sowden E, Pirie A. Barium and strontium concentrations in eye tissue. *Biochem J* 1958; **70:** 716–7.
9 Hunt VR. Concentrations of ^{210}Po ^{226}Ra and ^{228}Th in the choroid of the eye, particularly in cattle. In: Åberg S, Hungate FP, eds. *Radioecological concentration processes.* Oxford: Pergamon Press, 1967: 303–11.
10 Mole RH, Pirie A, Vaughan JM. Differential distribution of radioactive strontium and y trium in the tissues of the rabbit's eye. *Nature* 1959; **183:** 802–7.
11 Holtzman RB, Sha JY. ^{226}Ra and calcium in the human eye. Argonne National Laboratory Radiological and Environmental Research Division. *Annual Report July 1976–June 1977.* ANL 77–65, part 2: 72–6.
12 Dodo T. Review of thirty years study of Hiroshima and Nagasaki atomic bomb survivors' cataracts. *J Radiat Res (Tokyo)* 1975; **16** (suppl): 132–7.
13 Vaughan J, Bleanley B, Taylor DM. The distribution, excretion and the effects of plutonium as a bone seeker. In: Hodge HC, Stannard JN, Hirsch JB, eds. *Handbook of experimental Pharmacology.* New York: Springer, 1973: 349–502.
14 Rundo J, Holtzman RB. In: Jee WSS, ed. *The health effects of plutonium and radium.* Utah: JW Press, 1976: 497–504.
15 Hayes BP, Fisher RF. Influence of a prolonged period of low-dosage *x*-rays on the optic and ultrastructure appearances of cataract of the human lens. *Br J Ophthalmol* 1979; **63:** 457–64.
16 Otake M, Schull WJ. The relationship of gamma or neutron radiation to posterior lenticular opacities among atomic bomb survivors in Hiroshima and Nagasaki. *Radiat Res* 1982; **92:** 574–95.
17 Caird FI, Hutchinson M, Pirie A. Cataract in an English population. *Br J Prev Soc Med* 1965; **19:** 80–4.

18 International Commission on Radiation Protection. Recommendations of the International Commission on Radiological Protection. ICRP Publications 26. *Ann ICRP* 1977; **1:** 1–43.

19 International Commission on Radiation Protection. Statement and recommendations of the International Commission on Radiological Protection from its 1980 meeting. *Ann ICRP* 1980; **4:** 1–5.

20 Larsen RP, Oldham RO, Cacic CC, Farnham JE, Schneider JR. In: Rowland RE, Stehney AF, eds. *Radiological and Environmental Research Division Annual Report.* Part 2. Centre for Human Radiobiology, Argonne National Laboratory, Argonne, Illinois, 1979: 145–53.

21 Spiers FW. Radioisotopes in the human body, physical and biological aspects. *Am Inst Biol Sci Monogr Ser Radiat Biol.* New York: 1968.

22 Von Sallman L, Tobias CA, Auger HO, *et al.* Effects of high-energy particles, *x*-rays and aging on lens epithelium. *Arch Ophthalmol* 1955; **54:** 489–514.

23 Spiess H. ^{224}Ra induced tumours in children and adults. In: Mays CW, Jee WS, Lloyd RD, Stover BJ, Dougherty JH, Taylor GN, eds. *Delayed effects of bone-seeking radionuclides.* Salt Lake City: University of Utah Press, 1969.

24 Spiess H, Gerspach A, Mays CW. Soft tissue effects following ^{224}Ra injections into humans. *Health Phys* 1978; **35:** 61–81.

25 Wick RR, Muller WA, Linzner U. Distribution studies in mice of ^{224}Ra in colloidal (Peteosthor) and ionic preparations as used in human therapy. *Health Phys* 1983; **44** (suppl 1): 580–3.

26 Wick RR, Gössner W. Follow-up study of late effects in ^{224}Ra treated ankylosing spondylitis patients. *Health Phys* 1983; **44** (suppl 1): 187–95.

27 Löscher C. Cataract in radium dial painter. *Klin Monatsbl Augenheilkd* 1963; **142:** 743–7.

28 Adams EA, Brues AB, Anast GA. Survey of ocular cataracts in radium dial workers. *Health Phys* 1983; **44** (suppl 1): 73–9.

29 Baverstock KF, Papworth GD, Vennart J. Risks of radiation at low dose rates. *Lancet* 1981; **i:** 430–3.

30 Mole RH. The radiobiological significance of the studies with ^{224}Ra and thorotrast. *Health Phys* 1978; **35:** 167–74.

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Ocular dominance, reading, and spelling ability in schoolchildren

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SUMMARY The association of reading disability with perceptuomotor problems has had a chequered history. This study examines the relationship between a new test of ocular dominance and reading and spelling ability in a group of 298 schoolchildren. Similar rates for unstable ocular dominance were found for poor readers as in comparable studies. The rates of unstable ocular dominance did not differ between the 'dyslexics' and the controls. These findings in a blind study question the role of this test as a diagnosis of 'dyslexia.'

A number of studies of children with reading disabilities have suggested that they suffer from a perceptuomotor problem. In particular an association has been claimed between difficulties in sequential eye movements while following a series of light emitting diodes and reading disability.[1 2] More recently, however, a number of studies have failed to support the original contentions.[3 4] Furthermore there is some suggestion that the ability to track sequentially displayed lights is dependent on reading skill and the direction in which text has been read.[5]

The association of reading disability and a failure to establish a dominant eye has had a chequered history. Benton and his colleagues claimed to have found support for an association between unfixed ocular dominance and reading disability, but withdrew their claims in the light of contradictory research and their failure to show an association between improvement in reading and the development of dominance following eye occlusion.[6-8] More recently Stein and Fowler have reported an association between a new test of ocular dominance and reading disability which they suggest may account for the erratic eye movements some studies have found with 'dyslexics.'[9] They argue that 'dyslexia' may be associated with a failure to establish ocular dominance because it may lead to 'confusion about precisely where words and letters are positioned on a page.' These authors examined in detail 80 children who had been referred with reading problems to the Ophthalmology Department of the Royal Berkshire Hospital and found 63% of them to have unstable ocular dominance as determined by a modified Dunlop test. This form of assessment of ocular dominance is of the sensory variety, where some degree of conflict exists between the information transmitted to each eye. This type of ocular dominance test, in contrast to monocular sighting preference/dominance or acuity dominance, has received relatively little attention in the literature on reading disability.

The study reported in this paper re-examines the association between the test of ocular dominance used by Stein and Fowler and reading ability in schoolchildren where detailed information of the child's reading, spelling, and intellectual abilities were also gathered. The definition of 'dyslexia' is complicated, and we have followed Stein and Fowler in specifying reading and spelling ability in relation to chronological age. The group considered to be dyslexic are those who produce a reading or spelling performance at least 18 months behind their chronological age. In addition, in this study the measures of ocular dominance were all conducted in the absence of the examiner's (RH) having any knowledge of the child's reading or intellectual abilities.

Subjects and methods

The subjects consisted of 298 children aged 7–11 from various schools selected to participate in a larger study of reading. None of the children had been referred to any clinic for reading difficulties and

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none had any gross neurological defecit. The information gathered on each child consisted of a full intellectual assessment (WISC) and three reading tests to examine three levels of reading skill. The Schonell graded word spelling test was used to assess the ability to spell to dictation. The Schonell graded word reading test was used to examine the child's ability to read single words in isolation, and the Neale test provided a measure of accuracy in reading prose passages. Each of these tests yields a score which is then converted into a reading or spelling age. As is common in studies of 'dyslexia', no child was selected who had either a verbal or performance IQ of less than 90.

These tests were all conducted by a psychologist.

DUNLOP TEST

The test of ocular dominance used in this study was identical to that used by Stein and Fowler. This involves the child viewing two macular fusion slides through a synoptophore. The slide viewed by the right eye has a house with a small tree to the left of the front door, while in that viewed by the left eye a large tree appeared to the right of the door of the house. The trees were thus initially projected to the nasal retina of each eye. The subject adjusted a knob until the two slides were found to fuse. The subject then perceived a house with a small tree to the left (viewed by the right eye) and a large tree to the right of the door (viewed by the left eye). The tubes of the synoptophore were then separated and the subject's eyes diverged to retain fusion. The relationship of the trees to the house remained constant in each slide, but the subject gained a strong impression that one of the trees had moved. This test enables the eye whose ocular motor and retinal signals are associated to be identified and thus the dominant eye to be distinguished. In order to prevent the child from adopting a guessing strategy the slides were changed throughout the test. To ensure that a comparison would be possible with the other data relating this test to reading, the orthoptist conducting the examination was trained by Stein and Fowler.

The test was repeated 10 times, and the convention of scoring adopted by Stein and Fowler and followed in this paper is that if the dominant eye is located on the same side on eight or more occasions then the child is considered to have a fixed dominant eye. With scores of less than eight the child is considered to have unstable or unfixed dominance.

Results

1. Left and right eye, dominance. The number of subjects showing fixed right eye dominance (n=99) was significantly greater than the number showing left ocular dominance (n=52). This finding is consistent with other assessments of sensory dominance and, in fact, sighting preference/dominance.[10]

2. Eye dominance and spelling ability. It may be expected that spelling ability, with its requirement to resolve small spatial positions, would be the most sensitive reading index of any problems of ocular dominance.[10] The results shown in Figure 1 indicate the percentage of children with fixed and unfixed ocular dominance at various levels of spelling ability. Those with a spelling age of 18 months or more behind their chronological age would be classed as having specific spelling difficulties and would be expected to indicate a significantly smaller proportion of individuals with fixed ocular dominance. In contrast those whose spelling is advanced significantly above their chronological age would be expected to have a greater proportion of fixed dominance. Although the trend in these findings was in the direction predicted, the differences between groups was small and did not reach significance ($\chi^2=2{\cdot}74$; 3 df; $p>0{\cdot}05$). It is also worth noting that 37% of children with excellent spelling failed to show fixed ocular dominance.

The difference between the fixed and unfixed groups at each of the levels of spelling performance relative to chronological age displayed in Figure 1 were further examined by means of *t* tests. The groups were compared on verbal IQ, performance IQ, and age. The *t* tests failed to show any differences between the fixed and unfixed groups on either IQ measure. With the exception of one group, all the comparisons on age failed to indicate any significant differences. The exception was with the group whose spelling ability was 18 months ahead of their chrono-

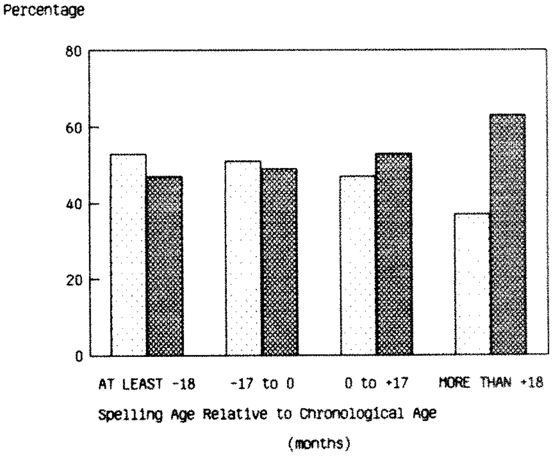

Fig. 1 *Ocular dominance and spelling.* ☐ *Unfixed: <8 trials indicating one eye dominant.* ▨ *Fixed: 8–10 trials indicating one eye dominant.*

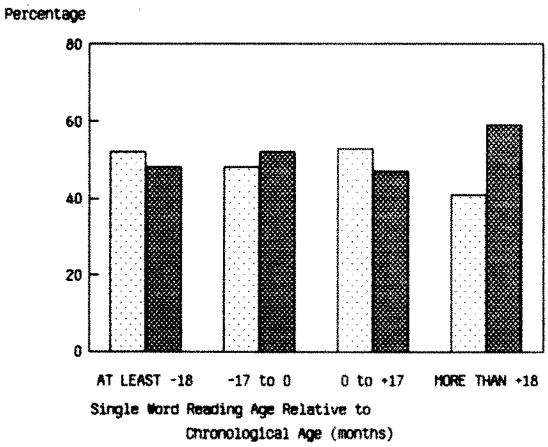

Fig. 2 *Ocular dominance and single word reading.* ☐ *Unfixed: <8 trials indicating one eye dominant.* ▨ *Fixed: 8–10 trials indicating one eye dominant.*

logical age ($t=2{\cdot}06$; df 28; $p<0{\cdot}05$). The mean age for those with fixed ocular dominance was five months less than those with unfixed dominance.

3. Eye dominance and single word reading. A similar analysis to that performed on the spelling data was conducted on the data for single word reading. These results are displayed in Figure 2. They fail to show any association between ocular dominance and difficulties in reading single words ($\chi^2=1{\cdot}75$; df 3; $p>0{\cdot}05$).

Further analysis of the fixed and unfixed groups at each of the levels of performance of single word reading shown in Figure 2 failed to indicate any differences between their verbal IQ, performance IQ, and age.

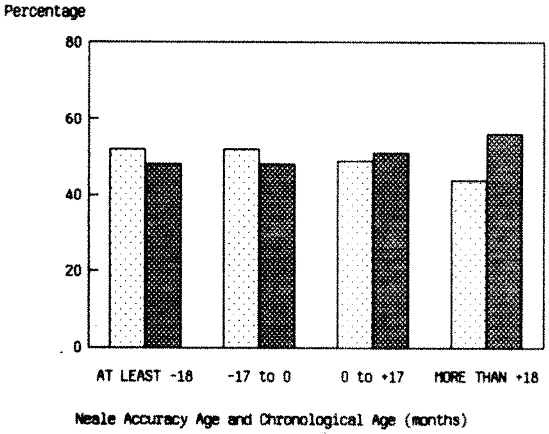

Fig. 3 *Ocular dominance and reading prose passages.* ☐ *Unfixed: <8 trials indicating one eye dominant.* ▨ *Fixed: 8–10 trials indicating one eye dominant.*

4. Eye dominance and reading prose passages. The analysis of the data from reading prose passages is shown in Figure 3. This analysis failed to show any significant association between reading prose passages and ocular dominance ($\chi^2=0{\cdot}99$; df 3; $p>0{\cdot}05$). 51% of the poor readers on this test failed to indicate fixed ocular dominance, while 44% of those who performed excellently on this test also indicated a lack of fixed ocular dominance.

The verbal IQ, performance IQ, and age of the fixed and unfixed ocular dominance groups were compared at each of the levels of reading prose passages relative to chronological age. With one exception these analyses failed to indicate any significant difference between these groups on these variables. The group who had unfixed ocular dominance and were 18 months behind their chronological age on the Neale test had a significantly higher performance IQ than those at the same level of reading performance with fixed ocular dominance.

5. Eye dominance and intelligence. A separate analysis was conducted to examine the relationship between ocular dominance and the two measures of intelligence. No significant differences were found between the proportion of fixed and unfixed individuals when the subjects were divided into three bands of IQ scores. These results are shown in Figures 4 and 5.

Discussion

The above data fail to confirm any association between this test of ocular dominance and spelling,

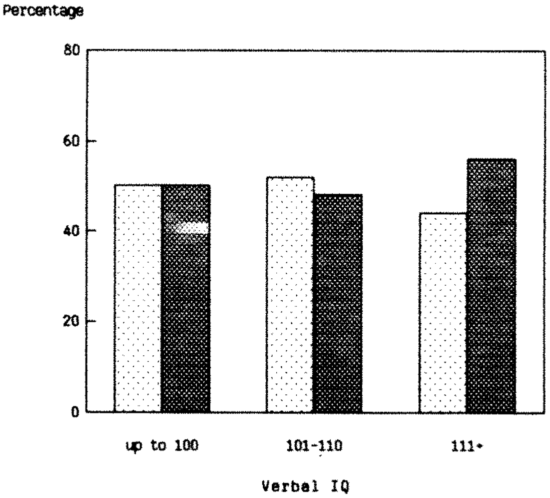

Fig. 4 *Performance IQ and ocular dominance.* ☐ *Unfixed: <8 trials indicating one eye dominant.* ▨ *Fixed: 8–10 trials indicating one eye dominant.*

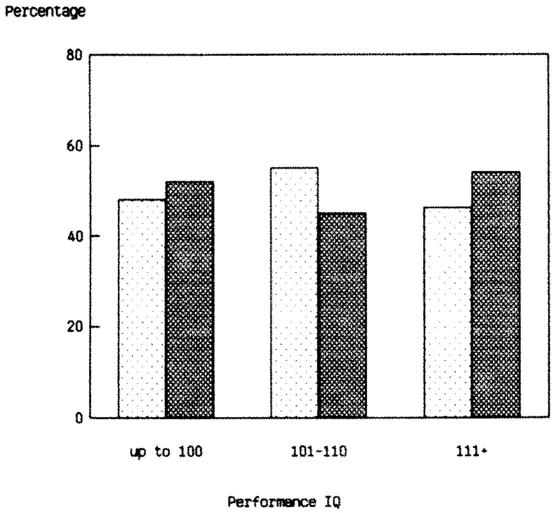

Fig. 5 *Verbal IQ and ocular dominance.* □ *Unfixed: <8 trials indicating one eye dominant.* ▨ *Fixed: 8–10 trials indicating one eye dominant.*

reading single words, and reading prose passages. The only suggestion of an association concerned the spelling test, but this failed to reach significance. In addition no significant tendency for fixed ocular dominance was found with increasing verbal or performance IQ. The detailed analysis of IQ and age at each level of reading and spelling performance failed to show any significant effects of these variable with fixed and unfixed ocular dominance.

In comparing our results with those of Stein and Fowler, it is important to point out that we are not in disagreement over the proportion of 'dyslexic' subjects who fail to establish fixed ocular dominance. They report data on two groups of 'dyslexics' who yielded 63% and 52% with unfixed ocular dominance. We found 54%, 52%, and 52% of individuals 18 months behind their chronological age on spelling, reading single words, and reading prose passages respectively, to have unfixed ocular dominance. Stein and Fowler report finding only 1 out of 80 of their normal subjects to have unstable ocular dominance. The findings reported above indicate that the proportion of individuals with fixed and unfixed ocular dominance do not differ according to spelling and reading ability. In fact a sizeable proportion of individuals who are particularly adept at these tasks still fail to indicate a stable ocular dominance on the test used by Stein and Fowler.

The most significant difference between our study and that performed by Stein and Fowler, which may go some way to account for the disparity of results, is that in this study the subjects were all examined by an orthoptist who had no knowledge of the child's performance on any of the other measures. In Stein and Fowler's study the 'dyslexic' children had been referred to a reading clinic and/or the ophthalmology department for reading problems. The 'normal' readers were selected from schools and matched to a subgroup of the 'dyslexics.' It appears that the testing was performed on different occasions and thus it is unlikely that it was performed blind.

In the present study the subjects were all selected from normal schools and the 'dyslexic' group was not restricted to those referred for either assessment or treatment. This difference does not appear to have significantly influenced the results, as in both studies the percentage of 'dyslexics' with unstable ocular dominance remained approximately the same.

The test of ocular dominance used in this study was the same as that in the Stein and Fowler study. Because the orthoptist's examination and the modified Dunlop test are difficult to perform and we wished to have our results comparable with those in their study, our orthoptist (RH) spent a period of time being trained by Fowler. Both were satisfied at the end of this training that the techniques of assessment were comparable.

We conclude on the basis of our study that ocular dominance as assessed by this version of the Dunlop test does not on its own have any direct relationship to reading and spelling performance of schoolchildren. In particular it does not discriminate between those who perform poorly and those with adequate or superior performance. We are currently analysing other measures of oculomotor and perceptual functioning in these subjects, and it is possible that a combination of unfixed ocular dominance and some other function may lead to reading difficulties.

We thank Dr John Stein and Sue Fowler for their assistance and advice as well as the time in training our orthoptist. We thank all the schools whose co-operation made this study possible. We also acknowledge the generous support of the Linbury Trust.

This research was supported by a generous grant from the Linbury Trust.

References

1 Pavlides G. Dyslexic's erratic eye movements. *Dyslexia Rev* 1978; **1:** 22–8.
2 Pavlides G. The 'dyslexia syndrome' and its objective diagnosis by erratic eye movements. In: Rayner K, ed. *Eye movements in reading*. New York: Academic Press, 1983.
3 Stanley G, Smith G, Hewell E. Eye-movements and sequential tracking in dyslexic and control children. *Br J Psychol* 1983; **73:** 181–7.
4 Olsen R, Kliegel R, Davidson B. Dyslexic and normal reader's eye movements. *J Exp Psychol* 1983; **9:** 816–25.
5 Newman SP, Civil M. Directional differences in eye tracking. Paper presented at the Second European Conference on Eye Movements, Nottingham, England. 1983.
6 Benton CD, McCann JW, Larsen M. Dyslexia and dominance. *J Pediatr Ophthalmol* 1965; **2:** 53–7.

7 Benton CD, McCann JW, Larsen M. A practical approach for the ophthalmologist. *J Pediatr Ophthalmol* 1968; **5:** 25–9.
8 Benton CD, McCann JW. Dyslexia and dominance. *J Pediatr Ophthalmol* 1969; **6:** 220–2.
9 Stein JF, Fowler S. Diagnosis of 'dyslexia' by means of a new indicator of eye dominance. *Br J Ophthalmol* 1982; **66:** 332–6.
10 Porac V, Coren S. The dominant eye. *Psychol Bull* 1976; **83:** 880–97.

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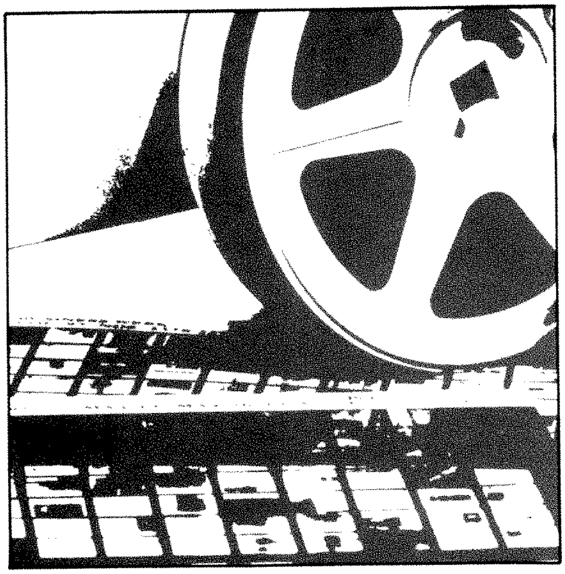

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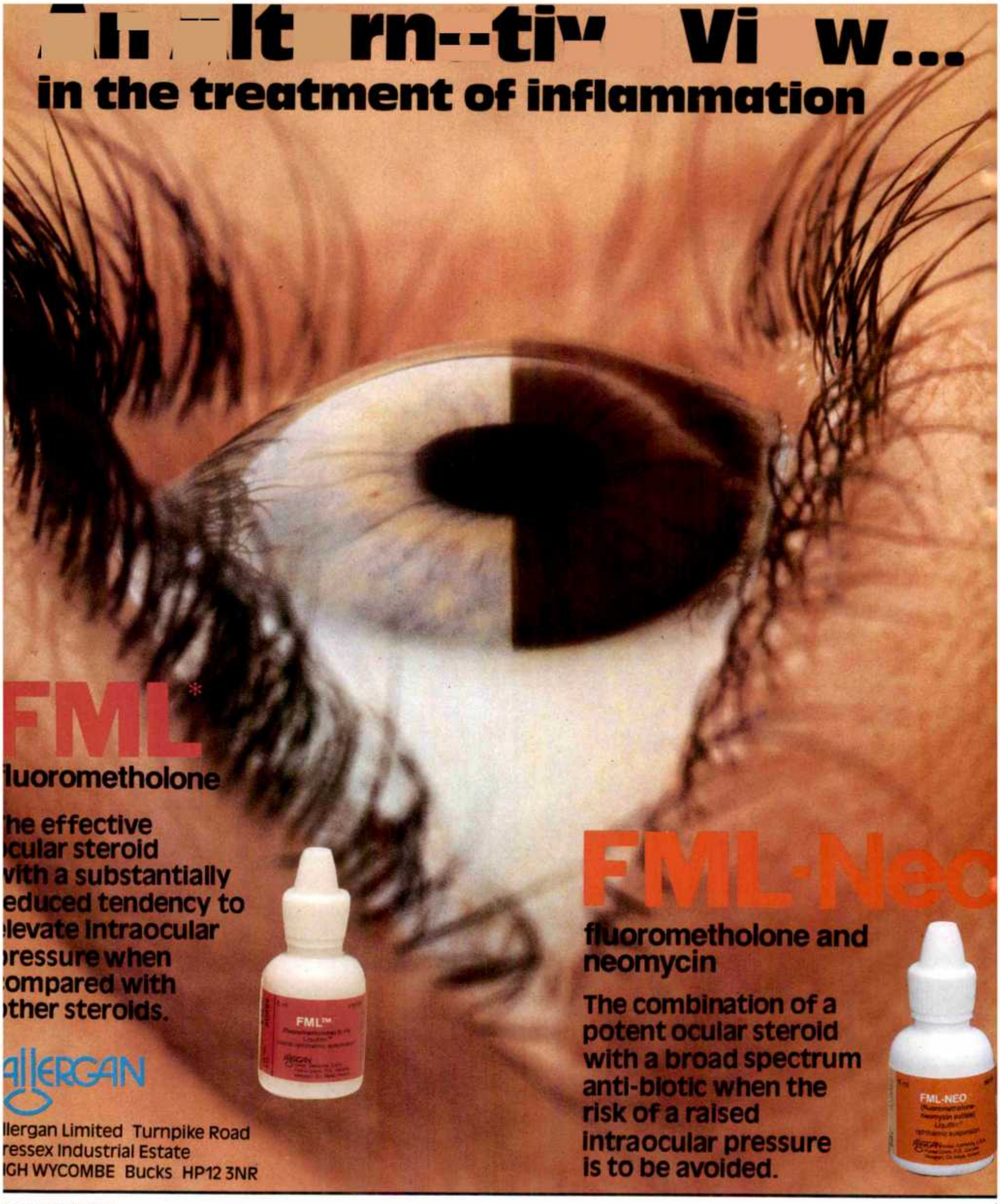

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Blue light hazard and aniridia

RICHARD V ABADI AND CHRISTINE M DICKINSON

From the University of Manchester Institute of Science and Technology, Manchester

SUMMARY The fundi of three patients with aniridia were photographed with a 470 nm illuminating light source. No apparent change in contrast was observable throughout the macular region. This would suggest an absence of the macular pigment. The likelihood of aniridics being more susceptible than normal persons to blue light damage is discussed.

In recent years the ocular hazards of non-ionising radiation have received great attention.[1-3] While the extent of light damage to the retina depends in the main on retinal irradiance level and exposure duration, many researchers have become increasingly aware of the role played by the wavelength of the source.[4 5] This has been clearly demonstrated in that light of wavelengths greater than 580 nm has been shown to produce predominantly thermal injuries, while photochemical effects are encountered with visible radiation of lower wavelengths (400–580 nm[6-11]).

The normally pigmented eye appears to be secure from possible blue light insult encountered in a natural environment because of the absorption characteristics of the cornea, crystalline lens, and macular pigment. Presumably if the situation arose such that one or more of these spectral filters were absent, the retina would be more susceptible to photochemical damage. Not surprisingly such cases do exist, for example, in the aphakic and also in the human albino (oculocutaneous and ocular), who not only lacks melanin in the pigment epithelium of the iris and the retina but also does not appear to possess any macular pigment.[12-17] In addition the fovea in albinos is often reported as being hypoplasic.[18 19]

Since poor foveal differentiation is also a frequent feature of the aniridic retina,[20-22] it was therefore the purpose of this study to ascertain if, like albinos, aniridics too lack xanthophyll pigment. As in our previous investigation, monochromatic fundus photography was employed to examine the macular area.[17 23 24]

Subjects and methods

A fundus camera (Zeiss) was used with its aperture stop constantly set at 5·5 mm. A blue gelatin bandpass filter (Ilford No. 602) with a maximum transmission at 470 nm was inserted into the illuminating system in order to visualise the xanthophyll pigment. Previous studies had established that this was a suitable method to establish the presence of xanthophyll. Flash intensities of 60 and 120 w sec^{-1} were used. Black and white ASA 125 film (Kodak Plus X) was used, and the films were commercially developed and printed with no retouching.

Three subjects with aniridia were examined. This small sample number of subjects reflects the low incidence of the condition, which is estimated to be 1 in 100 000.[20 26] In this study two of the three subjects were brothers. An extensive family history indicated an autosomal dominant mode of inheritance. Both the brothers had monocular visual acuities of less than 6/36, bilateral peripheral corneal pannus, bilateral small central lens opacities, and no visible irides. Infrared oculography revealed that they both showed a manifest latent nystagmus with associated superimposed horizontal pendular oscillation. Our third subject had no family history of ocular disorder and monocular visual acuities of 6/18+1. A bilateral peripheral corneal pannus and a small unilateral (right eye) central lens opacity were present. No iris was visible. No ocular oscillation could be detected by infrared oculography.

Twenty-five subjects with no ocular or systemic disease acted as controls.

Results

Examination of the retina with the 470 nm illuminating wavelength revealed two distinct patterns. Firstly, a macular darkening with an increased contrast area around the fovea was found in all normal subjects regardless of their skin pigmentation (Fig. 1). The smaller central region is believed to

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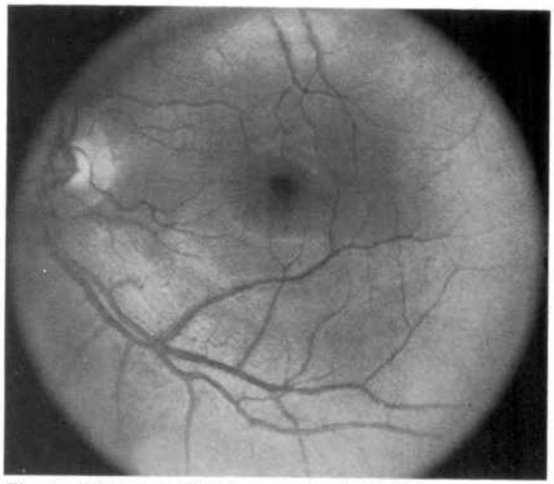

Fig. 1 *The normal fundus examined with 470 nm illuminating wavelength to enhance the contrast of the macular pigment. Notice the marked macular darkening, indicating the presence of macular pigment.*

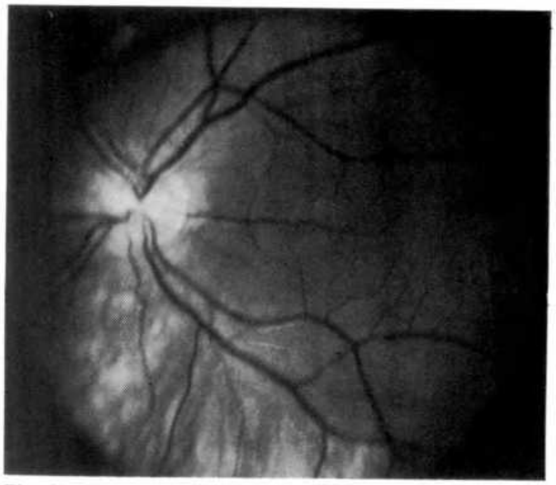

Fig. 2 *The aniridic fundus examined with a 470 nm illuminating wavelength. There is no apparent change in contrast throughout the macular region, suggesting that there is an absence of macular pigment.*

correspond to the high absorption of blue light by the xanthophyll pigment. This has been described previously.[17 23 24]

On the other hand there was no apparent change in contrast throughout the macular region in the three aniridics, suggesting an absence of macular pigment in these subjects (Fig. 2).

Discussion

The syndrome of congenital aniridia may show at least four phenotypes. The first type, to which our three patients belong, is the association of aniridia with foveal hypoplasia, nystagmus, corneal pannus, and the likelihood of secondary glaucoma. The second type is that reported by Elsas *et al.*[25] where visual resolution appears relatively preserved. The third and fourth phenotypes are intimately associated with mental deficiency[26] and Wilms's tumour[27] respectively.

For our subjects the retinal irradiance level is increased because of the presence of large and constant pupil aperture. This represents a substantial incremental increase in the light flux as the retinal irradiance is a function of the square of the pupil diameter. Of course additional parameters such as the transmission of the ocular media and the degree of defocus of the retinal image need to be taken into account when evaluating the absolute irradiance level.

Large fixed pupil apertures also disqualify the visual system from being optically ideal.[28] Yet, though the retinal image quality is degraded by optical aberrations, the Stiles-Crawford effect, and a reduced depth of focus, the loss of visual resolution at photopic illumination levels is only about 18%[29]—that is, a decrease in visual acuity from 6/6 to 6/7·5. Indeed Elsas and his colleagues have described a large pedigree with familial aniridia in which 61% of patients had visual acuities of 6/9 or better and only 5% had visual acuities <6/60.[25] None had nystagmus or corneal pannus, while only 18% of the patients had some degree of lenticular opacity. Thus the absence of iris tissue alone cannot be solely responsible for the poor acuity usually associated with aniridia.

A static pupil does, however, possess two important disadvantages. The first concerns the loss of the pupil light reflex. Constriction of the natural pupil at high light levels reduces the retinal illumination and so ensures a more rapid dark adaptation process in the retina to low light levels, as well as improving sensitivity and contrast detection during dark adaptation. Indeed experiments have shown that the dark adaptation process is speeded up by 4–10 min and the sensitivity initially increased by approximately 10 times.[30]

Secondly, the retinal irradiance cannot be controlled. This feature has led some clinicians to propose that the lack of macular development in aniridia may be caused by excessive amounts of light entering the eye.[31] Although nystagmus should have the effect of limiting the duration of exposure of the fovea, this would apply only to a point source, whereas most natural blue light sources are extended. Thus there is a case for fitting an aniridic patient with some form of artificial pupil (for example, an iris print contact lens) to minimise the possible long-term effects of light damage, particularly for wavelengths of 400–500 nm.[5] Moreover the optical portion could also be tinted, so that the absorption properties of the contact lens parallel that of xanthophyll, thus providing further protection for the retina. Similar safeguards may also be advisable for the albino individual.

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References

1 Sliney DH, Freasier B. The evaluation of optical radiation hazards. *Appl Optics* 1973; **12:** 1–24.

2 Lanum J. The damaging effects of light on the retina. Empirical findings, theoretical and practical implications. *Surv Ophthalmol* 1978; **22:** 221–49.

3 Lerman S. Radiant energy and the eye. London: Bailliere and Tindall, 1980.

4 Mainster MA, Ham WT, Delori FC. Potential retinal hazards. Instrument and environmental light sources. *Ophthalmology* 1983; **90:** 927–32.

5 Sliney DH. Eye protective techniques for bright light. *Ophthalmology* 1983; **90:** 937–43.

6 Ham WT, Mueller HA, Sliney DH. Retinal sensitivity to damage from short wavelength light. *Nature* 1976; **260:** 153–5.

7 Ham WT Jr, Retinal sensitivity to short wavelength light. *Nature* 1976; **262:** 629–30.

8 Marshall J, Weale RA. Retinal sensitivity to short wavelength light. *Nature* 1976; **262:** 629–30.

9 Lawwill T, Crockett S, Currier G. Functional and histologic measures of retinal damage in chronic light exposure. *Doc Ophthalmol* 1977; **15:** 285–95.

10 Ham WT, Mueller HA, Ruffolo JJ, Clarke AM. Sensitivity of the retina to radiation damage as a function of wavelength. *Photochem Photobiol* 1979; **29:** 735–43.

11 Ham WT Jr, Ruffolo JJ Jr, Mueller HA, Guerry Du Pont III. The nature of retinal radiation damage: dependence on wavelength, power level and exposure time. *Vision Res* 1980; **20:** 1105–11.

12 Deutman AF. The hereditary dystrophies of the posterior pole of the eye. Springfield: Thomas, 1971: 10–4.

13 O'Donnell FE Jr, Hambrick W Jr, Green WR, Illiff J, Stone DL. X-linked ocular albinism: an oculocutaneous macromelanosomal disorder. *Arch Ophthalmol* 1976; **94:** 1883–92.

14 Fulton AB, Albert DM, Craft JL. Human albinism: light and electron microscopy study. *Arch Ophthalmol* 1978; **96:** 305–10.

15 O'Donnell FE, King RA, Green WR. Autosomal recessively inherited ocular albinism affecting females as severely as males. *Arch Ophthalmol* 1978; **96:** 1621–5.

16 Nussbaum JJ, Pruett RC, Delori FC. Historic perspectives—macular yellow pigment. The first 200 years. *Retina* 1981; **1:** 296–310.

17 Abadi RV, Dickinson CM. Monochromatic fundus photography of human albino. *Arch Ophthalmol* 1983; **101:** 1706–11.

18 Nettleship E. Note on some varieties of albinism. *Trans Ophthalmol Soc UK* 1906; **26:** 244–50.

19 Usher CH. Histological examination of an adult human albino's eyeball with a note on mesoblastic pigmentation in foetal eyes. *Biometrika* 1920; **13:** 45–56.

20 Duke-Elder S. *System of ophthalmology*. St Louis: Mosby, 1963: **3** (2).

21 Hermann JS, Koverman JJ. Prophylaxis of amblyopia in aniridia. The role of pinhole contact lenses. *J Pediatr Ophthalmol* 1968; **5:** 48–52.

22 Anderson SRY, Geertinger P, Larsen HW, *et al.* Aniridia, cataract and gonadoblastoma in mentally retarded girl with deletion of chromosome 11: a clinico-pathological case report. *Ophthalmologica* 1978; **176:** 171–7.

23 Delori FC, Gragoudas ES. Examination of the ocular fundus with monochromatic light. *Ann Ophthalmol* 1976; **8:** 703–9.

24 Delori FC, Gragoudas ES, Francisco R, Pruett RC. Monochromatic ophthalmoscopy and fundus photography. I. The normal fundus. *Arch Ophthalmol* 1977; **95:** 861–8.

25 Elsas FJ, Maumenee IH, Kenyon KR, Yoder F. Familial aniridia with preserved ocular function. *Am J Ophthalmol* 1977; **83:** 718–24.

26 Warburg M, Mikkelson M, Andersen SRY, *et al.* Aniridia and interstitial deletion of the short arm of chromosome 11. *Metab Pediatr Ophthalmol* 1980; **4:** 97–102.

27 Fraumeni JF, Glass AG. Wilms's tumor and congenital aniridia *JAMA* 1968; **206:** 825–8.

28 Charman WN. The retinal image in the human eye. In: Osborne N, Chader G, eds. *Progress in retinal research.* Oxford: Pergamon Press, 1983: **2:** 1–50.

29 Woodhouse JM. The effect of pupil size on grating detection at various contrast levels. *Vision Res* 1975; **15:** 645–8.

30 Woodhouse JM, Campbell FW. The role of the pupil light reflex in aiding adaptation in the dark. *Vision Res* 1975; **15:** 649–53.

31 Potts AM. Society proceedings. *Am J Ophthalmol* 1961; **51:** 161–77.

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Obituary

Baron Professor Jules François

In paying tribute to a unique personality in the field of ophthalmology it is of the greatest importance to emphasise his many personal attributes. Born in 1907 in Gingelom in Belgium, Jules François studied medicine at the University of Louvain and in Paris. In 1942 he became associate professor and in 1948 was appointed professor of ophthalmology at the University of Ghent. Since that time he has been awarded numerous international medals, has received honours from countries all over the world, and has made a remarkable number of contributions to the literature, his interests embracing ophthalmic medicine, surgery, genetics, pathology, and physiology. These span a period of over 50 years, from his early papers in 1931 to his most recent publications in 1984.

Throughout his life as an ophthalmologist Jules François has taken advantage of his agile mind to extend the borders of ophthalmic knowledge, and to take with him to these border areas many younger colleagues who have benefited from his teaching and from his helpful advice in forming their careers.

He was fluent in several European languages, and never failed to learn some of the phrases of the native tongue of any country he visited, so that he could feel he was at one with his hosts, and could show his appreciation of their invitations in the manner they most easily understood. His generous hospitality to his guests in Belgium, and in particular at his lovely home in Ghent, will be remembered by many hundreds of his colleagues visiting there with their societies, with the International Council, or on personal occasions. At any meeting Jules would greet warmly everyone whom he knew, and there were very few who were strangers to him, and those not for long.

It is well known that the record of his activities is formidable, and to say this is enough without attempting to dwell upon more than a few of his achievements. Among those that he must have cherished were his presidency of the International Council of Ophthalmology from 1974 to 1982, and his election in 1982 to honorary life presidency of the council. He was awarded the Gonin medal in 1966, a singular honour 'presented periodically to the ophthalmologist who has contributed most lavishly to the advancement of ophthalmology.'

He was the first recipient of the Duke-Elder international medal in 1982, a medal presented jointly by the founder of the Duke-Elder Fund (Lady Duke-Elder) and the International Council of Ophthalmology in honour of the memory of Sir Stewart Duke-Elder. This Jules must have cherished in an especially personal way, as he and Stewart and Phyllis Duke-Elder held a strong mutual affection for one another. He was without doubt happy to have succeeded such a close friend as Sir Stewart as honorary life president of the International Council.

He was honoured with the personal title of Baron on 14 November 1983. This was a graceful acknowledgement of the contribution he had made to ophthalmology in Belgium.

Already during his lifetime there have been tributes to Jules François in the form of lectureships and the establishment of the foundations in his name. In his honour a Jules François gold medal has now been created to reward ophthalmological works of high scientific level.

The death of Jules François on 13 August 1984 has deprived the world of ophthalmology of an outstanding figure. When writing to his colleagues his form of address was always 'Dear Friend', and it is to one such dear friend that every ophthalmologist pays tribute. JRH

Notes

Glaucoma group

TRAVEL FELLOWSHIP

The Glaucoma Group Travel Fellowship, sponsored by Merck Sharp and Dohme, will assist a visit to a hospital or research centre during the academic year starting 1 October 1985. The award will be equivalent to £1500 sterling. The purpose of the award is to enable the successful applicant to gain experience and knowledge in pursuit of a specific project related to glaucoma.

RESEARCH GRANT

The Glaucoma Group Research Grant, sponsored by the International Glaucoma Association, will be available for a clinically orientated research project related to glaucoma for 1985. The award will be equivalent to £2500 sterling. The Grant may be used towards salary or project expenses or for buying equipment.

Both these awards are available to medical graduates and non-medical scientists resident in the United Kingdom or Republic of Ireland. They may be held concurrently with other awards. Applicants should send a curriculum vitae with information on their research project and details for proposed visit (preferably with confirmation from the centre/s visited) to: Dr S Nagasubramanian, Glaucoma Group Secretary, Glaucoma Unit, Moorfields Eye Hospital, High Holborn, London WC1V 7AN. The closing date for applications for these awards is 14 June 1985. The successful candidate will be informed by August 1985.

Facial surgery

The Interspecialty Facial Surgery Congress for Aesthetic, Cancer, and Reconstructive Surgery will be held at the Waldorf-Astoria, New York, on 24–27 April 1985. Details from Mr James F Pawlak, c/o Pierre Guibor, MD, 630 Park Avenue, New York, NY 10021, USA.

Anne Allerton Fund

A charity has been set up called the Anne Allerton Fund. The income from the fund is to be used in any sphere of ophthalmic research. Applications for grants should be sent before 1 May 1985 c/o The Anne Allerton Fund (reference 06), 100 Fetter Lane, London EC4A 1BN. Grants will be considered between £3000 and £10 000 per annum. Applicants should submit full details of their projects and indicate where the monies are required.

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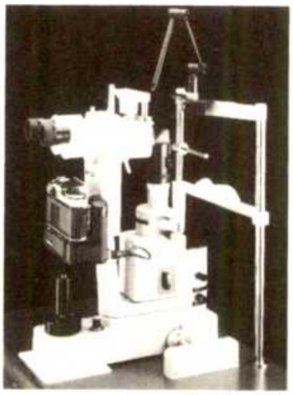

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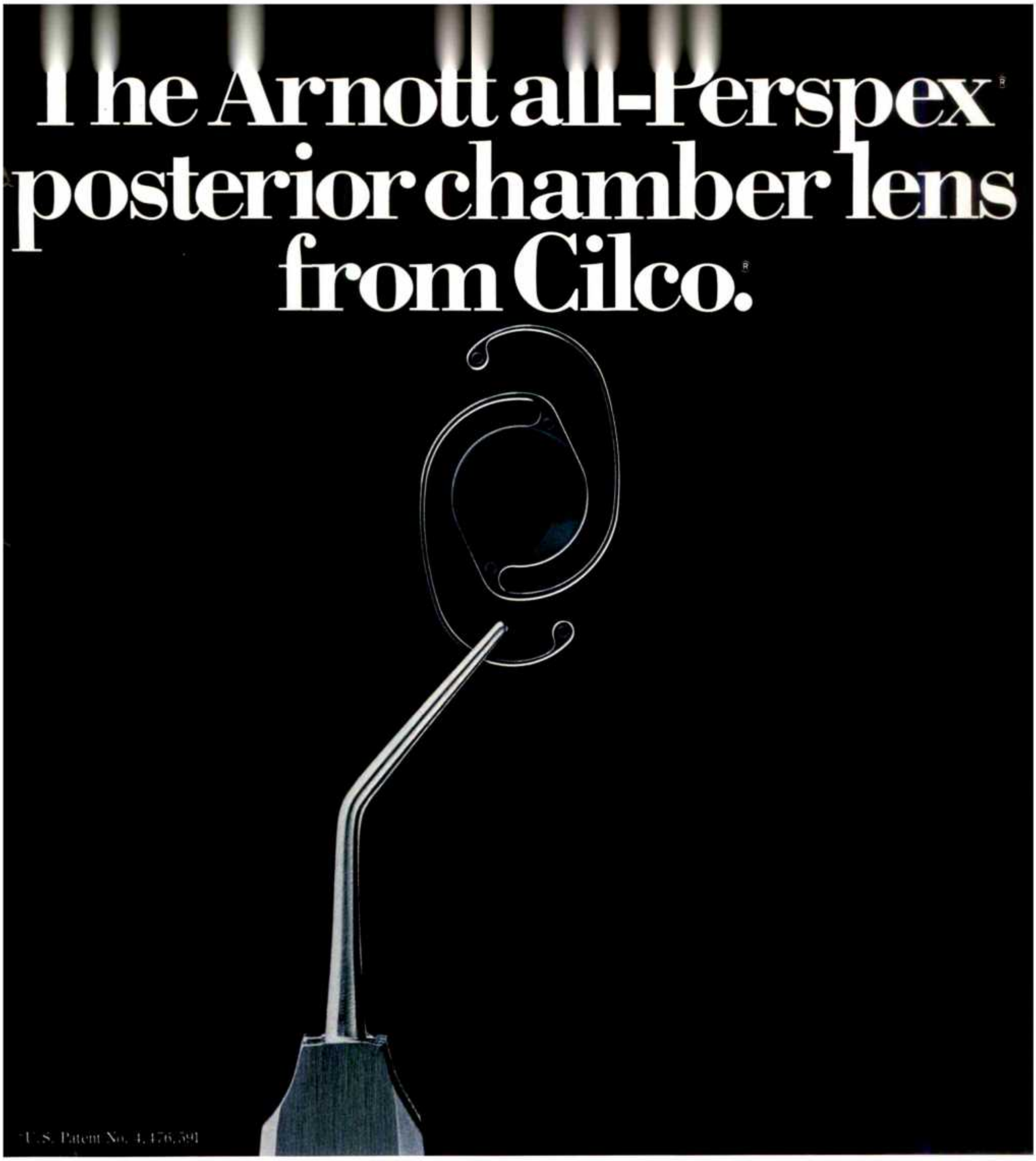

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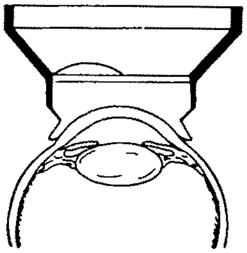

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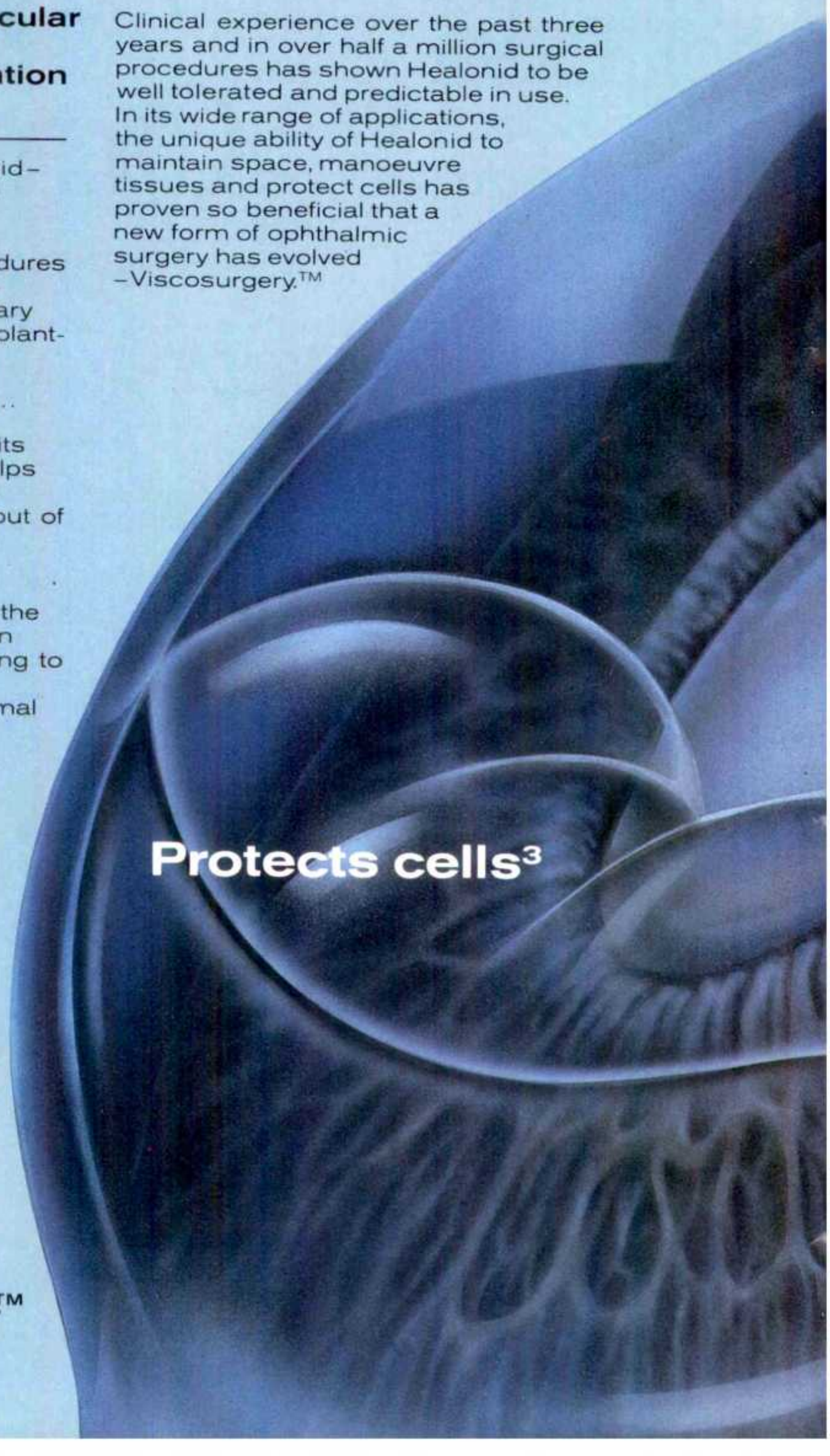

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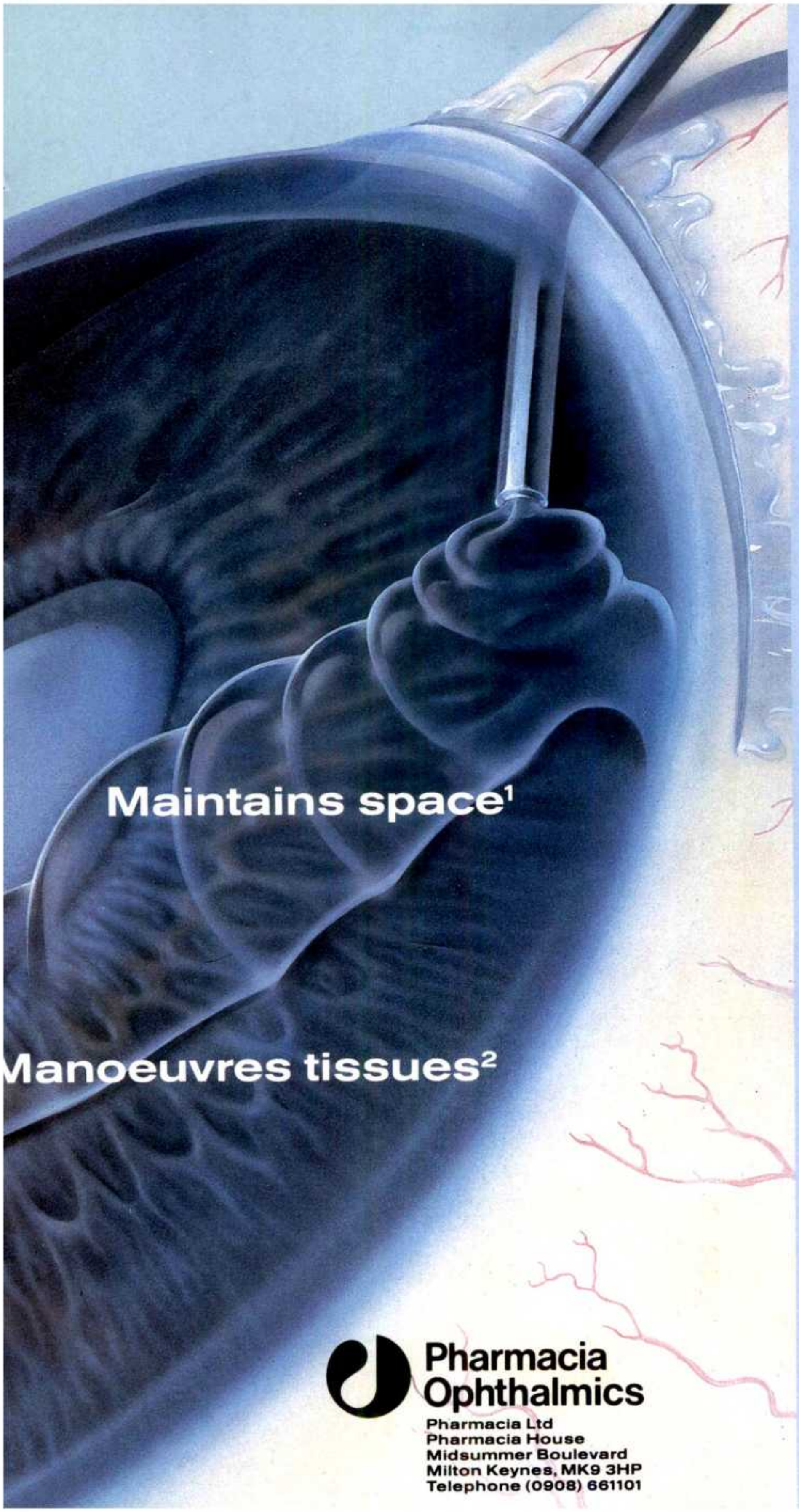

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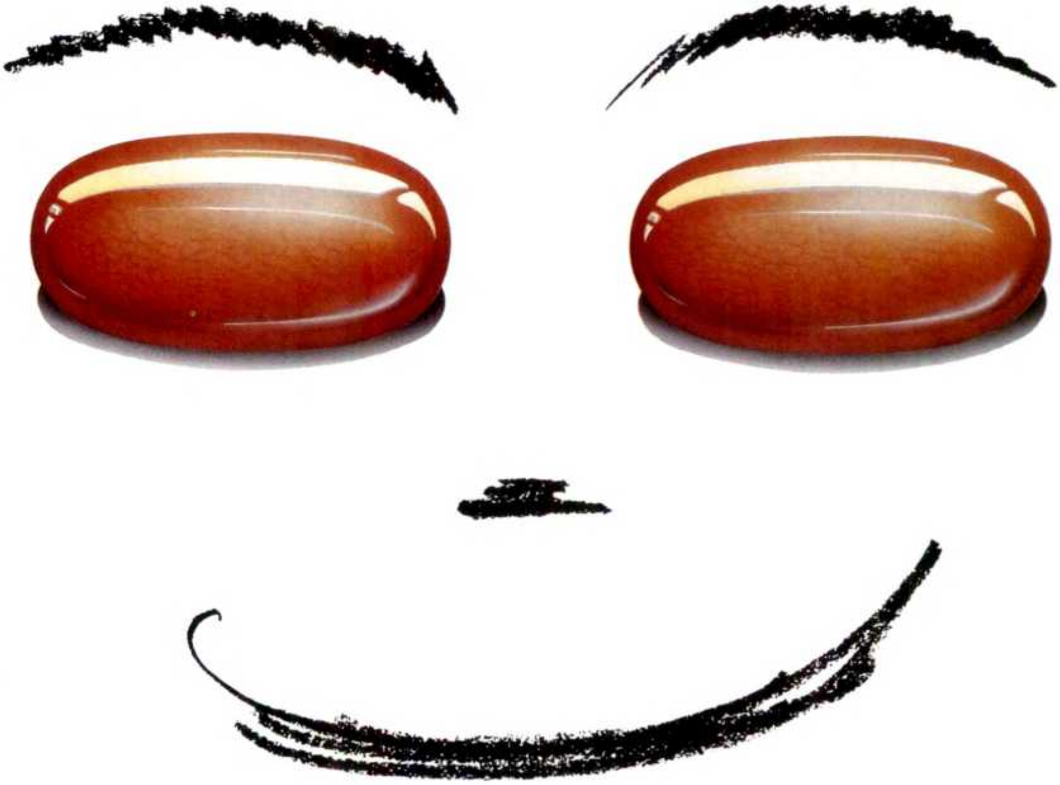

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References:

1. Garner LL, et al, Amer. J. Ophthalmol. 1963 **55,** 323-327.
2. Duke Elder, WS, Textbook of Ophthalmology as quoted in: Moses, RA, Adlers Physiology of the Eye, 1975: 192.

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British Journal of Ophthalmology, 1985, **69**, 237–239

Do we need a retinal pigment epithelium (or choroid) for the maintenance of retinal apposition?

WALLACE S FOULDS

From the Tennent Institute of Ophthalmology, University of Glasgow

SUMMARY The relative rarity of retinal detachment following extensive surgical resection of choroid and retinal pigment epithelium for choroidal malignant melanoma is discussed in relation to the factors maintaining retinal apposition under these circumstances.

Many structural and dynamic factors have been suggested as being of importance in the maintenance of retinal apposition with its bed.[1 2] These include interdigitation of retinal receptor cell outer segments with the apical processes of the retinal pigment epithelium (RPE), the presence of the interphotoreceptor matrix between the outer retina and the RPE,[3] and active transport of molecules from the potential subretinal space to the choroid by cells of the RPE.[4] All these suggested mechanisms presuppose either a structural or functional role for the RPE in the maintenance of retinal apposition.

Experience of local resection of choroidal melanoma has indicated that surgical removal of extensive areas of choroid and RPE does not commonly lead to retinal detachment, and the significance of this finding is discussed in this paper.

Materials and methods

The technique used by the author for the local surgical resection of choroidal melanomas has been previously described[5-7] and has now been applied in more than 100 cases. The technique involves the surgical removal of affected choroid and related RPE together with a half thickness deep lamella of sclera adjacent to the choroid containing the tumour. The overlying retina is separated from the tumour and in most instances remains intact. The wall of the eye is reconstituted by the outer lamella of sclera, which has been temporarily raised as a flap to allow access to the affected choroid and related deep scleral lamella.

Whether there is a preoperative retinal detachment or not—and the presence of an exudative detachment is of course common in cases of choroidal melanoma—it is a constant finding that in the immediate postoperative period the retina is flat and in contact with the scleral bed (Figs. 1 and 2). Flattening of the retina does not appear to be dependent on the area of resection and occurs even where up to one-third of the choroid and RPE has been removed (Fig. 3).

Occasionally a tumour is adherent to the overlying retina, and in these cases a full thickness breach of the retina may occur during surgical removal of the tumour. In spite of this, retinal flattening on to the scleral bed is still the rule provided the retinal hole is over the resected area.

Sometimes late retinal detachment has been seen where vitreous haemorrhage has led to the development of preretinal fibrosis and traction (in the absence of a retinal break) or very occasionally where

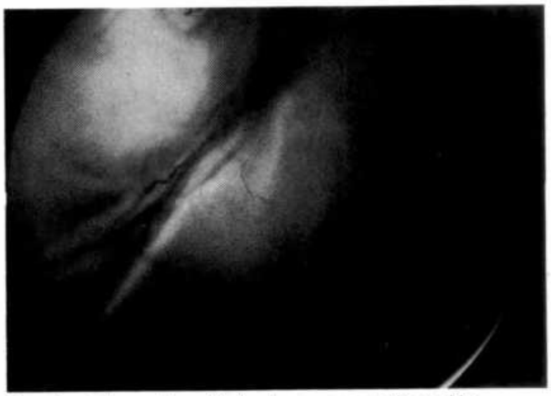

Fig. 1 *A large choroidal melanoma complicated by extensive retinal detachment. The tumour was treated by local surgical excision.*

Correspondence to Professor W S Foulds, Tennent Institute of Ophthalmology, Western Infirmary, Glasgow G11 6NT.

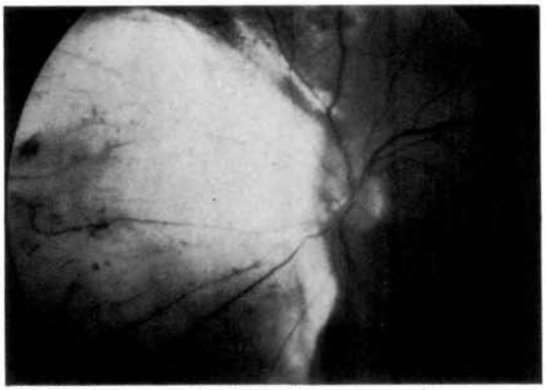

Fig. 2 *Same eye as Fig. 1 showing postoperative appearance. The retina is now flat and remains in contact with bare sclera in the surgical coloboma.*

a full thickness retinal tear has been situated at the edge of the resected area rather than centrally. In these cases the previously flat retina has separated from the underlying scleral bed without evidence of acquired adhesion between the retina and bare sclera.

Results

Of the first 90 cases of local resection for choroidal melanoma there was subsequent retinal detachment in 14 cases. In nine instances the retinal detachment was the result of vitreous organisation and traction and unassociated with a detected retinal break. In two of these cases retinal reattachment followed closed pars plana vitrectomy and fluid gas exchange. In five cases the retinal detachment was a complication of retinal hole formation close to the resected area. In four of the five cases retinal reattachment followed conventional detachment surgery.

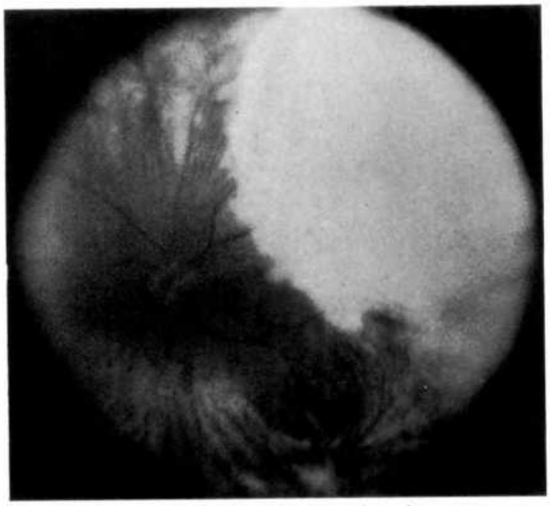

Fig. 3 *Wide-angled fundus photograph to show postoperative appearance after local surgical resection of a very large choroidal tumour. The surgical coloboma involves one-third of the choroid and pigment epithelium but the overlying retina remains flat and in contact with bare sclera.*

Discussion

The results in cases of local choroidectomy show that even a previously detached retina will flatten on to bare sclera after surgical removal of choroid and RPE and in most cases remain in contact with the scleral bed, even though no actual adhesion may form between retina and sclera. It is interesting to speculate on the forces involved in this retinal apposition with the sclera.

It is known that in the normal animal eye small molecules injected into the vitreous (xenon,[8] tritiated water[9]) largely leave by passing across the retina and RPE to reach the choroid. Each of these structures offers resistance to the passage of small molecules, and we and others have determined the flow conductivity of retina,[10] combined retina, RPE, and choroid,[11] and sclera.[12] Not unexpectedly the sclera has a higher resistance per unit area to the passage of water than does either retina or combined retina, RPE, and choroid.[11]

We have shown that there is a small movement of water and other tracers from the vitreous out through the sclera, but in the intact eye this is at most only 2·4% of total tracer injected into the vitreous.[13]

The rate of molecular movement from the subretinal space to the choroid across the RPE is significantly increased following metabolic damage to the RPE by intravenously injected sodium iodate,[14] suggesting that intact RPE acts as a barrier in relation to the outward movement of molecules from the subretinal space. Any such barrier will undoubtedly be destroyed when the RPE is surgically removed.

As a working hypothesis it is suggested that the reduction in scleral thickness, which is an inherent component of the technique used for the surgical resection of malignant melanoma, may decrease scleral resistance and increase transscleral flow. The removal of choroid and RPE will in addition remove any resistance in these tissues to the passage of fluid from the potential subretinal space to the sclera. Under these circumstances the relative flow conductivities of the retina and of the surgically thin sclera would be important. If fluid escaped transsclerally at a rate which was potentially greater than its complementary movement across the retina, then a small pressure difference on either side of the retina would be generated and might be sufficient to maintain the retina in apposition with the sclera. It seems unlikely, especially in larger resections, that the intact RPE at the edge of the surgical coloboma could empty the subretinal space laterally to maintain the required apposition.

That the resulting apposition of retina with the sclera is maintained by functional rather than structural forces is suggested by the occasional late occurrence of retinal detachment as a complication of preretinal traction or a retinal break not situated immediately over the resected area. In those cases where this has occurred the retina appears to have become detached from the scleral bed without apparently having established any structural union with it.

The fact that a full thickness retinal break when situated over the resected area is not as a rule complicated by retinal detachment postoperatively is surprising. It is possible that in some cases tamponade of the break by formed cortical vitreous may maintain a sufficient resistance to the passage of water from the vitreous cavity to the potential subretinal space.[15] An alternative explanation might relate to the mathematics of water movement through the retinal break relative to water movement through the sclera. A similar mechanism has been postulated and subjected to mathematical investigation in the case of retinal flattening after episcleral plombage where a retinal hole is not in contact with the indentation at the end of the surgical procedure.[16] In the case of local resection of choroidal tumours, however, it has been the author's experience that even large retinal breaks when situated over the site of choroidal resection are not usually complicated by retinal detachment. In the case of large breaks a relatively faster clearance of subretinal fluid than its recruitment through the retinal break would seem an unlikely explanation for retinal flattening, and vitreous tamponade of the retinal hole appears a more acceptable explanation.

Whatever the explanation for retinal apposition with the scleral bed following extensive surgical resection of the choroid and RPE for choroidal malignant melanoma, it is useful that retinal detachment is a relatively uncommon complication of this surgical technique.

I am grateful to Mrs A Currie, senior technician in the Tennent Institute, for the photographs, and to Mrs J Murray for typing the manuscript.

References

1 Foulds WS. Aetiology of retinal detachment. *Trans Ophthalmol Soc UK* 1975; **95:** 118.

2 Marmor MF, Tonnies M. Local environmental factors and retinal adhesion in the rabbit. *Exp Eye Res* 1982; **34:** 727–33.

3 Berman ER. Mucopolysaccharides (glycosaminoglycans) of the retina—identification, distribution and possible biological role. *Mod Probl Ophthalmol* 1969; **8:** 5–31.

4 Strambach DA, Marmor MF. The rate and route of fluid resorption from the subretinal space in the rabbit. *Invest Ophthalmol Visual Sci* 1982; **22:** 292–302.

5 Foulds WS. The local excision of choroidal melanomata. *Trans Ophthalmol Soc UK* 1973; **93:** 343–6.

6 Foulds WS. Experience of local excision of uveal melanomas. *Trans Ophthalmol Soc UK* 1977; **97:** 412–5.

7 Foulds WS. Current options in the management of choroidal melanoma. *Trans Ophthalmol Soc UK* 1983; **103:** 28–34.

8 Moseley H, Foulds WS. The movement of xenon-133 from the vitreous to the choroid. *Exp Eye Res* 1982; **34:** 169–79.

9 Moseley H, Foulds WS, Allan D, Kyle PM. Routes of clearance of radioactive water from the rabbit vitreous. *Br J Ophthalmol* 1984; **68:** 145–51.

10 Fatt I, Shantinath K. Flow conductivity of retina and its role in retinal adhesion. *Exp Eye Res* 1971; **12:** 218–26.

11 Moseley H. Studies of fluid movement in the eye. PhD thesis. University of Glasgow 1980: 95–6.

12 Fatt I, Hedbys BO. Flow of water in the sclera. *Exp Eye Res* 1970; **10:** 243–9.

13 Moseley H, Johnson NF, Foulds WS. Vitreo-scleral fluid transfer in the rabbit. *Acta Ophthalmol (Kbh)* 1978; **56:** 769–76.

14 Neji A, Marmor MF. The resorption of subretinal fluid after diffuse damage to the retinal epithelium. *Invest Ophthalmol Visual Sci* 1983; **24:** 1475–9.

15 Foulds WS. The vitreous in retinal detachment. *Trans Ophthalmol Soc UK* 1975; **95:** 412.

16 Hammer ME. Retinal re-attachment forces created by absorption of sub-retinal fluid. In: Zauberman H, ed. Proceedings of the Conference on Sub-retinal Space 1979. *Doc Ophthalmol Proc Ser* 1981; **25:** 61–75.

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Retinal function of the diabetic retina after argon laser photocoagulation assessed electroretinographically

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SUMMARY Electroretinographic (ERG) responses were measured in diabetic patients before, during, and after panretinal photocoagulation treatment with argon laser. The laser applications reduced considerably the amplitudes of the a and b waves of the ERG. Moreover, the relationship between the amplitude of the b wave and that of the a wave was severely affected, resulting in ERG responses of abnormal pattern. The b waves were smaller than expected from the a waves. These findings indicated that the photocoagulation treatment not only destroyed the retinal areas directly illuminated by the laser beam, but also affected the functional integrity of adjacent areas. These additional effects resulted in subnormal signal transmission from the photoreceptors to the proximal retina.

Panretinal photocoagulation (PRP) has become an accepted treatment for diabetic retinopathy aimed at reducing the risk of blindness.[1] The intention of this therapy is to destroy a substantial portion of the peripheral retina in order to reduce the difference between oxygen demand and oxygen supply and thus to reduce the stimulus for neovascularisation.[2] The extent of retinal destruction by the PRP treatment may determine its effectiveness. The electroretinogram (ERG) reflects retinal activity as a mass response and is generally used as an objective index of retinal function.[3 4] Therefore many investigators have measured the electrical responses of the diabetic retina after photocoagulation.[5–10] In these studies the amplitudes of the a and b waves were used as criteria for retinal destruction. There was no agreement among the different studies. In one report a 10-95% b wave deterioration was observed in different patients who were treated similarly.[6] This variability was explained by variability in the extent of the effective retinal ablation. Similar lack of direct relationship between the number of laser applications and the reduction in the ERG amplitude was reported by others.[7] Another report concluded that the a wave was reduced more than the b wave,[8] thus supporting the notion that the laser application destroyed primarily the photoreceptors. These findings were later challenged in a study where both the b wave and the a wave were proportionally reduced.[9] Furthermore, some of the studies concluded that the ERG responses were reduced more than expected on the basis of the coagulated area,[6 8 10] while others stated that ERG reduction was proportional to the coagulated retinal area.[5 9]

In this study the ERG responses were measured in diabetic patients before, during, and after treatment with argon laser. The relationship between the amplitude of the b wave and that of the a wave was used as an index of retinal function.[11] This relationship was used to determine the integrity of signal transmission from the photoreceptors to the proximal retina.[11] Moreover, this method of ERG analysis circumvented problems arising from differences, between experimental sessions, of the flash intensities reaching the retina, due, for instance, to differences in pupil dilatation.[11] The data indicated that the photocoagulation treatment destroyed a substantial portion of the peripheral retina, causing a severe reduction in the ERG responses. In addition the laser treatment affected adjacent retinal areas and caused deterioration of signal transmission from the photoreceptors to the proximal retina. This finding explained previous reports of larger reductions in the b wave amplitude than expected on the basis of the coagulated area.

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Materials and methods

SUBJECTS

Electroretinographic responses were measured in 23 diabetic patients ranging in age from 30 to 70 years. In 16 patients ERG records were obtained only after panretinal photocoagulation (PRP) with argon laser. In these patients both eyes underwent PRP treatment. In seven patients the effects of the PRP treatment were followed in detail by recording the ERG responses before, during, and after treatment. In these subjects the ERG was also measured one week, one month, and if possible also six months after treatment, in order to ensure reliable recordings without the possible effects from retinal oedema caused by the laser treatment. These seven patients underwent PRP treatment in only one eye, either because the fellow eye had been treated before or because treatment was not mandatory.

ELECTRORETINOGRAM

The procedure for ERG recordings has been reported previously.[11] The electrical signals were recorded between a Henkes-type contact lens electrode (Medical Work Shop) and a reference electrode attached to the subject's forehead. The ground electrode was placed on the ear lobe. Uniform illumination of the retina by the test flash was achieved with a −100 dioptre lens attached to the contact lens electrode. An electronic camera flash was used for photostimulation. The intensity and colour of the test flash were controlled by 'neutral' density filters and broad-band colour filters (Schott).

The subject's pupil was maximally dilated by 0·5% cyclopentolate hydrochloride and 2·5% phenylephrine hydrochloride. The ERG responses were first recorded in the light-adapted state with background illumination of 11 foot-lamberts (38 cd/m^2). After 25 minutes of dark adaptation the ERG responses evoked by flashes of different intensities were recorded. Rod function was measured by a dim blue test flash.

ERG analysis included comparison of the a and b wave amplitudes measured in each response. The a wave amplitude was measured from the baseline to the trough of the a wave. The b wave amplitude was measured from the trough of the a wave to the peak of the b wave.

PANRETINAL PHOTOCOAGULATION

Panretinal photocoagulation in diabetic patients suffering from either preproliferative or proliferative diabetic retinopathy was performed in the usual manner with the pulsed argon laser (Britt). An average of 2500 applications was done, divided into five to six sittings. For each patient the laser beam was adjusted to produce similar retinal burns. The laser beam parameters were within the following ranges: energy, 300 mW to 1·8 W; duration 0·02 to 0·1 second; and spot size, 200 to 500 µm. PRP was performed in a scattered pattern, beginning by encircling the posterior pole and then covering a quadrant per session from the nasal side and clockwise. Some of the patients were admitted to hospital and treated daily until satisfactory coverage of the whole retina was achieved. Others were treated on an outpatient basis, with intervals of some days between sittings. Eyes were selected for PRP treatment either if they showed preproliferative retinopathy where areas of non-perfusion could be demonstrated by fluorescent angiography or if they showed neovascularisation on the disc (NVD) or neovascularisation elsewhere (NVE). Patients who underwent treatment in only one eye were chosen only on clinical considerations. In these cases the degree of retinopathy differed significantly between the two eyes. In all cases the untreated eye was treated, if necessary, at a later date.

Results

The ERG responses shown in Fig. 1 were recorded from one diabetic patient who underwent panretinal photocoagulation treatment of the right eye. Each pair of responses contains the ERG response recorded from the left (upper trace) and the right (lower trace) eyes. The responses in Fig. 1 were obtained before photocoagulation treatment was started (first column), after 900 laser applications to the right eye (second column), after treatment to the right eye was completed (third column), and six months after PRP was completed (fourth column). This patient was admitted to hospital and therefore received laser applications almost daily. ERG measurements were done in this and in other patients in hospital 24 hours after completion of each photocoagulation session. Since in this study we were interested in retinal function based on the entire dynamic range of the ERG, only dark-adapted responses were considered and are illustrated in Fig. 1. The responses in the first row were obtained by dim blue flash (4 log units attenuation) and therefore represented rod function. The responses in the second and third rows were evoked by white flashes attenuated by either a 3 log unit (second row) or a 1 log unit (third row) filter. As is evident in Fig. 1, the ERG responses of the right (treated) eye decreased significantly in amplitude after the laser treatment, while the responses measured from the left (untreated) eye varied only slightly between different experimental sessions. In all seven patients studied the ERG responses of the untreated eye were characterised by normal pattern and amplitude. However, normality was not satisfied

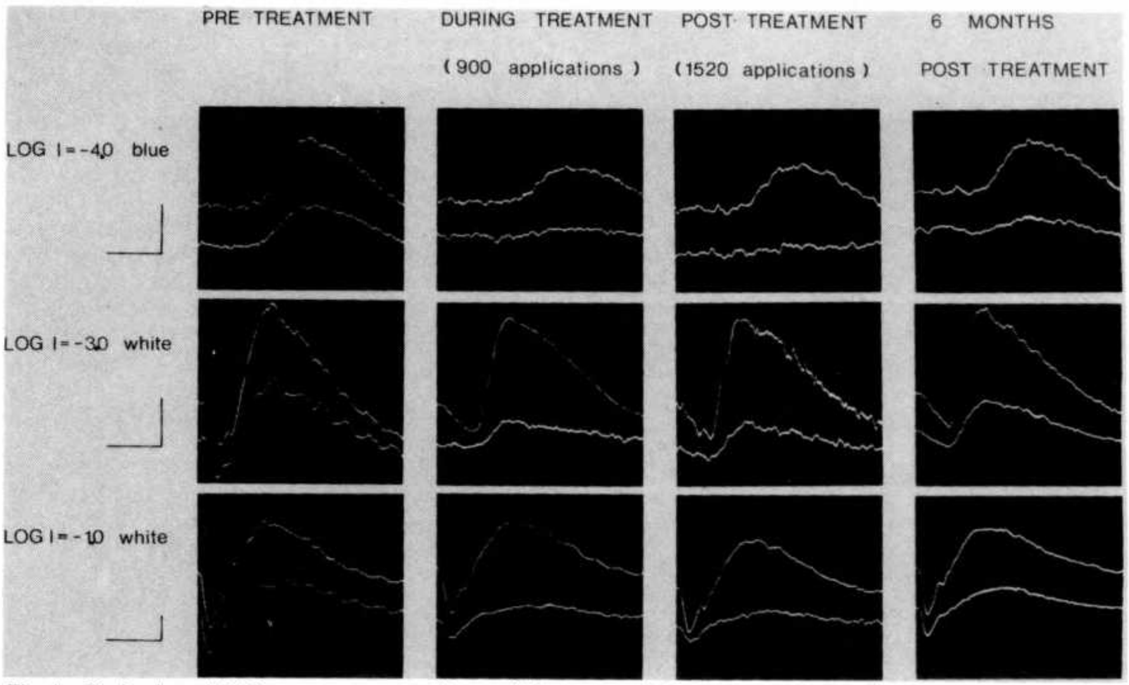

Fig. 1 *Dark-adapted ERG responses measured in one diabetic patient. Each pair of responses (OS: upper trace; OD: lower trace) was evoked by either dim blue flash (upper row), white flash of moderate intensity (middle row), or bright white test flash (lower row). The relative intensity of the flash is described by the 'neutral' density attenuation to the left of each row of responses. The ERG responses were obtained before PRP treatment (first column), during treatment after 900 laser applications had been delivered (second column), immediately after treatment (total of 1520 applications) was ended (third column), and six months after the PRP treatment (fourth column). The calibration bars to the left of each row of responses have a height of 200 μV and a length of 50 ms.*

by every parameter; the oscillatory potentials were usually subnormal.

Fig. 2 shows the effects of the photocoagulation treatment on the ERG responses. The reduction in the ERG amplitude was calculated from either the post-treatment/pretreatment amplitude ratio (Fig. 2A) or the treated eye/untreated eye amplitude ratio (Fig. 2B). The data are given as a function of the number of laser applications. In order to minimise the possible contribution of retinal oedema to the reduction in the ERG amplitude, ERG data were also measured one week, one month, and six months after completion of the PRP treatment and are shown in Fig. 2. The reduction of the ERG amplitude was calculated from responses evoked by flashes of different intensities. Reduction in the rod function was obtained from responses evoked by blue flash attenuated by a 4 log unit filter (open triangles). The white flashes used were bright enough to evoke responses containing both a and b waves. Therefore the reduction in these waves was calculated separately. In Fig. 2 open symbols describe b wave data, while solid symbols describe a wave data. Two different white flashes were used, one attenuated by a 3 log unit filter (circles) and the other by a 1 log unit filter (squares). It is apparent that the degree of retinal destruction calculated from ERG data strongly depended on the intensity of the test flash used to evoke the ERG responses. Estimates of retinal destruction also depended on whether the a wave or the b wave was used for its calculation. No consistent differences were found here between a and b wave reductions, contrary to previous findings of larger reduction in a wave than in b wave.[8]

Detailed examination of the ERG data after PRP treatment revealed that the b wave was usually reduced to a value which in the normal retina was not expected to be preceded by an a wave. To illustrate this observation the relationship between the b wave and the a wave for one diabetic patient is plotted in Fig. 3. The continuous curve bounded by the two dotted curves describes the normal mean±SD obtained from ERG data measured in 20 volunteers with normal retinal function.[11] The data points were obtained from ERG responses measured before treatment (circles), during treatment (triangles), and

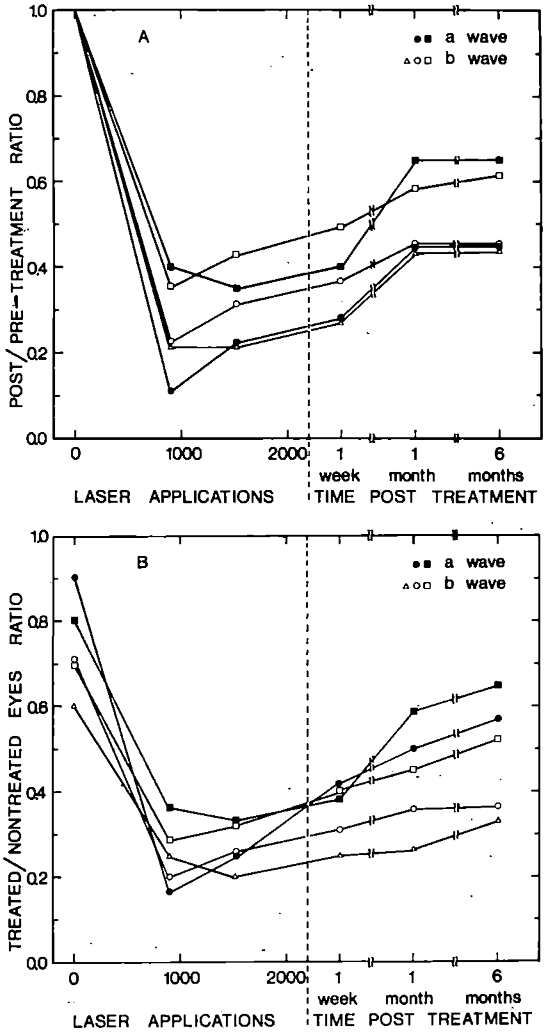

Fig. 2 *The effect of PRP treatment on the amplitude of the ERG responses. The reduction in the ERG is described either relative to the pretreatment values of the treated eye (A) or by comparing the treated eye to the untreated one as measured in each experimental session (B). The reduction in the ERG is shown first as a function of the number of laser applications delivered and then as a function of time after the PRP procedure was finished. The data points describe the reduction of the a wave (solid symbols) and the b wave (open symbols). The ERG responses used to construct the figure were elicited by dim (4 log units attenuation) blue flashes (open triangles), white flashes attenuated by a 3 log unit filter (circles), and white flashes attenuated by a filter of 1 log unit (squares).*

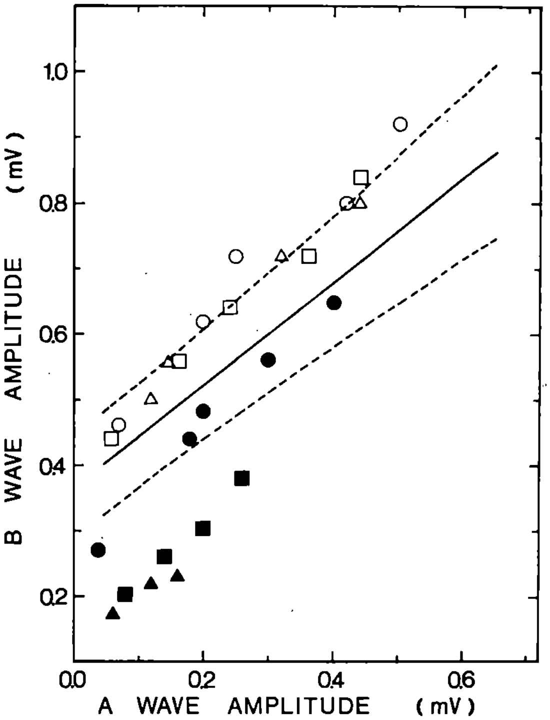

Fig 3 *The relationship between the b wave amplitude and the a wave amplitude. The mean normal relationship (continuous curve) is bounded by two dashed curves which describe the normal range (±2 SD). Data are given for the treated (solid symbols) and untreated (open symbols) eyes of one diabetic patient. Each set of symbols describes one experimental session. The ERG responses were measured before PRP treatment (circles), during the treatment period (triangles), and one month after termination of treatment (squares).*

one month after PRP treatment had been completed (squares). The b wave/a wave relationship of the untreated eye (open symbols) was within the normal range or slightly above it and did not change significantly between different experimental sessions. Data from the treated eye obtained before treatment (solid circles) were significantly different from the untreated eye data (open circles) but still within the normal range. ERG responses recorded from the treated eye in the middle of the treatment period (solid triangles) and one month after completion of the treatment (solid squares) showed not only reduction in the amplitude of the ERG but also a significant change in its pattern. The b wave/a wave relationship reduced significantly—that is, the b wave measured was significantly smaller than the value expected from the a wave amplitude.

This finding was quantified by using the a wave as the independent variable that depended only on the light intensity reaching the retina and the functional integrity of the photoreceptors. Thus for each ERG response the measured a wave was used to obtain the amplitude of the b wave expected from a normally

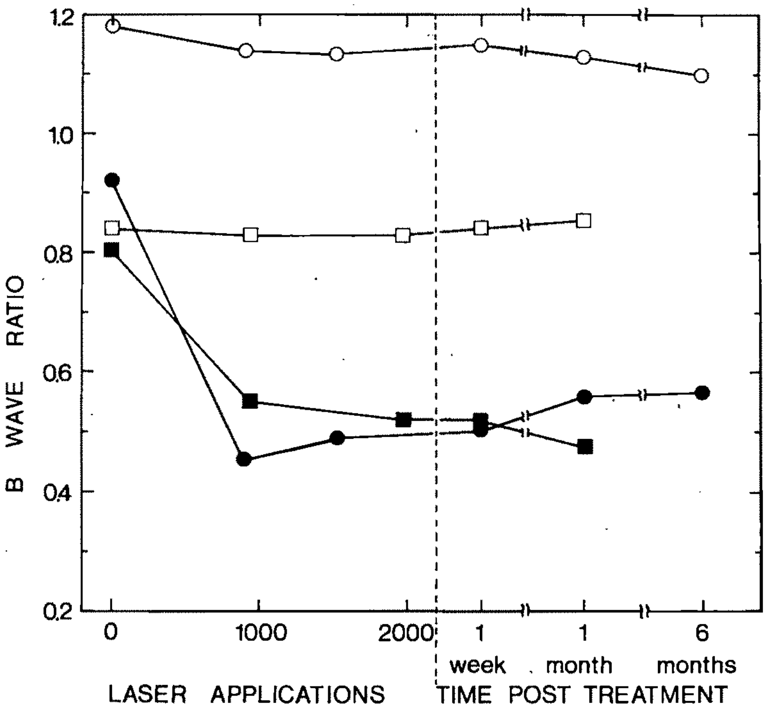

Fig. 4 *The effect of PRP treatment on the functional integrity of the retina. The b wave ratio is the ratio between the measured b wave and the value expected according to the a wave. The expected b wave was obtained from the normal b wave/a wave relationship. Each data point describes the average b wave ratios calculated for the individual ERG responses recorded from one eye in one experimental session. The b wave ratio is given as a function of the number of laser applications and also as a function of time after the PRP treatment was completed. The data were measured from both the treated (solid symbols) and the untreated (open symbols) eyes of two diabetic patients (squares and circles).*

functioning retina (Fig. 3, continuous curve). The ratio between the measured amplitude of the b wave and the expected value was averaged for all the responses obtained in each experimental session from one eye. This average, defined as the b wave ratio, was used as a quantified measure of the function of the diabetic retina. In Fig. 4 the b wave ratios for the treated (solid symbols) and untreated (open symbols) eyes are shown for two diabetic patients. Each data point was calculated from one ERG session from all the ERG responses measured in one eye that contained both a and b waves. The b wave ratio was calculated as a function of the number of laser applications from the ERG responses recorded at different stages of the PRP treatment. Data were also obtained one week, one month, and six months after completion of the treatment. The b wave ratios calculated for the two eyes before treatment differed significantly in one patient (circles) and slightly in the other one (squares). This was expected, since the eyes suffered from different degrees of retinopathy. The eye chosen for laser treatment was suffering from more advanced retinopathy than the fellow eye.

In all seven patients studied the eye scheduled for PRP treatment, based on clinical criteria, was also characterised by a smaller b wave ratio—that is, there was a correlation between the fundus appearance and the ERG data. Laser photocoagulation significantly reduced the b wave ratio to a level that stayed relatively constant throughout the treatment period and even six months after treatment had been completed. The b wave ratios of the untreated eyes varied slightly between experimental sessions. Comparison between the b wave ratios calculated for the treated and untreated eyes of six diabetic patients is given in Table 1. One patient who was studied here had previously undergone PRP treatment in one eye, and therefore his data were excluded from Table 1. Before PRP treatment both eyes showed normal b wave ratios, indicating normal signal transmission in the retina. After treatment was completed the b wave ratio of the untreated eye did not change, while that of the treated eye declined significantly, indicating inferior signal transmission from the photoreceptors to the proximal retina.

Retrospective examination of ERG data from 23 diabetic patients who underwent PRP treatment in both eyes revealed an average b wave ratio of 0·509±0·111 (SD). This value was significantly below the

Table 1 *B wave ratio for treated and untreated eyes in six diabetic patients*

	Treated eye (mean±SD)	*Untreated eye (mean±SD)*
Pretreatment	0·861±0·069	0·867±0·167
Post-treatment	0·563±0·062	0·859±0·173

normal value of 1·01±0·1 (SD) obtained from 20 volunteers with normal retinal function. These diabetic patients were examined electroretinographically because they either were scheduled for vitrectomy or had severe visual loss which could not be explained based on clinical data. These findings therefore supported the conclusion that photocoagulation by argon laser reduced signal transmission in the retina.

Discussion

The ERG responses were measured before, during, and after unilateral PRP treatment with argon laser in seven diabetic patients. The ERG parameters usually used to determine retinal function are the amplitudes of the a and b waves. However, it has been shown here that evaluation of the extent of retinal destruction could not be done reliably by comparing either the b wave or the a wave amplitude with the values measured in the treated eye before treatment or to the values obtained from the untreated eye. The extent of retinal damage thus calculated depended on the flash intensity used to evoke the ERG responses. In general the brighter the flash used the smaller the reduction observed in retinal function.

An additional parameter for the ERG analysis, the b wave/a wave relationship, was found most useful in evaluating the loss of retinal function induced by the laser treatment. This relationship is based on the assumption that the a wave depends on the light intensity reaching the retina and the functional integrity of the photoreceptors. The b wave depends on the a wave and on signal transmission from the photoreceptors to the proximal retina.[11] Therefore any interference limited to the light pathway or to the photoreceptor function is not expected to affect the b wave/a wave relationship.[11] It has been shown in this report that laser applications significantly reduced the b wave/a wave relationship of the treated eye (Fig. 3). The b wave ratio of the treated eye was found to be within the normal range before treatment started, suggesting a normal signal transmission in the retina. The reduction in the b wave ratio caused by the laser treatment indicated that the non-coagulated retina responded abnormally to light stimuli and that this impairment was expressed by a significantly smaller b wave than expected from the measured a wave. This observation is supported by data published previously.[9] In Table 5 of that report scotopic ERG data were given for eyes treated with argon laser. In all the patients the post-treatment responses showed a subnormal b wave/a wave relationship, while most cases (7 of 10) showed a normal b wave/a wave relationship before treatment. These findings suggested that the argon laser applications had two major effects on the retina: the laser pulses destroyed retinal tissue directly illuminated and also reduced signal transmission in adjacent retinal areas. Histological support for this conclusion has been obtained from a checkerboard coagulation applied to the rabbit retina, where degeneration of the retina was also observed between coagulated areas.[12]

The conclusion that the laser applications also affected the non-coagulated retinal areas explains previous reports in which the b wave reduction was found to be larger than expected from the estimated area of the coagulated retina.[6 8 10] The b wave, which is a summed response of the entire retina, is severely reduced by PRP treatment, owing to direct destruction of retinal tissue. The additional reduction in the b wave, which cannot be accounted for by the coagulated retina, is caused by defective signal transmission in the non-coagulated areas. Another observation that can be explained by the data presented here was the finding that the a wave was more affected than the b wave by the photocoagulation treatment.[8] This observation contradicted Granit's general comment that any interference (with the exception of alcohol) with the retina would affect the b wave more than the a wave.[13] It was argued that the selective effect of the laser treatment on the a wave reflected its direct destructive effects on the photoreceptors.[8] Similar conclusions could be drawn here from the data presented in Fig. 2A. Examination of the ERG responses evoked by flash intensity of −3·0 log relative units revealed that the a wave (solid circles) was reduced by the photocoagulation treatment to a larger extent than the b wave (open circles). This differential effect was apparent only when the amplitudes of the b and a waves were considered separately and were compared with the pre-treatment values without account being taken of the relationship that existed between these waves in the normal ERG. In view of the normal b wave/a wave relationship (Fig. 3), a 50% reduction of the a wave —for instance, from 200 μV to 100 μV caused by destruction of photoreceptors only—is expected to cause a reduction of the b wave from 524 μV to 444 μV, namely, by about 15%. If the b wave is reduced to a greater extent, as was found here and previously,[5-10] it implies that the b wave is more affected by the laser treatment than is the a wave. It can be concluded, therefore, that the reduction in the a wave due to the direct destructive effects of the laser upon the photoreceptors should cause only a proportional reduction in the b wave, according to the normal b wave/a wave relationship. The additional reduction observed in the b wave is due to subnormal signal transmission from photoreceptors to the proximal retina in non-coagulated areas.

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References

1 Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. *Ophthalmology* 1978; **85:** 82–106.

2 Krill AE, Archer DB, Newell FW, Chishti MI. Photocoagulation in diabetic retinopathy. *Am J Ophthalmol* 1971; **72:** 299–321.

3 Armington JC. *The electroretinogram.* New York: Academic Press, 1974.

4 Berson EL. Electrical phenomena in the retina. In: Moses RA, ed. *Adler's physiology of the eye.* St Louis: Mosby 1981: 466-529.

5 Frank RN. Visual fields and electroretinography following extensive photocoagulation. *Arch Ophthalmol* 1975; **93:** 591–8.

6 Ogden TE, Callahan F, Riekhof FT. The electroretinogram after peripheral retinal ablation in diabetic retinopathy. *Am J Ophthalmol* 1976; **81:** 397–402.

7 François J, De Rouck A, Cambie E, Castanheira-Dinis A. Electrophysiological studies before and after argon laser photocoagulation in diabetic retinopathy. *Ophthalmologica* 1978; **176:** 133–44.

8 Gjötterberg M, Blomdahl S. Human electroretinogram after argon laser photocoagulation of different retinal areas. *Ophthalmol Res* 1981; **13:** 42–9.

9 Liang JC, Fishman GA, Huamonte FU, Anderson RJ. Comparative electroretinograms in argon laser and xenon arc panretinal photocoagulation. *Br J Ophthalmol* 1983; **67:** 520–5.

10 Lawwill T, O'Connor PR, ERG and EOG in diabetics pre- and post-photocoagulation. In: *Proceedings of the tenth ISCERG Symposium, Los Angeles, 1972.* The Hague: Junk, 1973: 17–23.

11 Perlman I. Relationship between the amplitudes of the b wave and the a wave as a useful index for evaluating the electroretinogram. *Br J Ophthalmol* 1983; **67:** 443–8.

12 Schuurmans RP, De Lege WA, Van Lith GHN, Oosterhuis JA. The influence of photocoagulation of the retina on the electroretinogram. *Doc Ophthalmol* 1977; **42:** 369–73.

13 Granit R. *Sensory mechanisms of the retina.* London: Hafner, 1963: 55.

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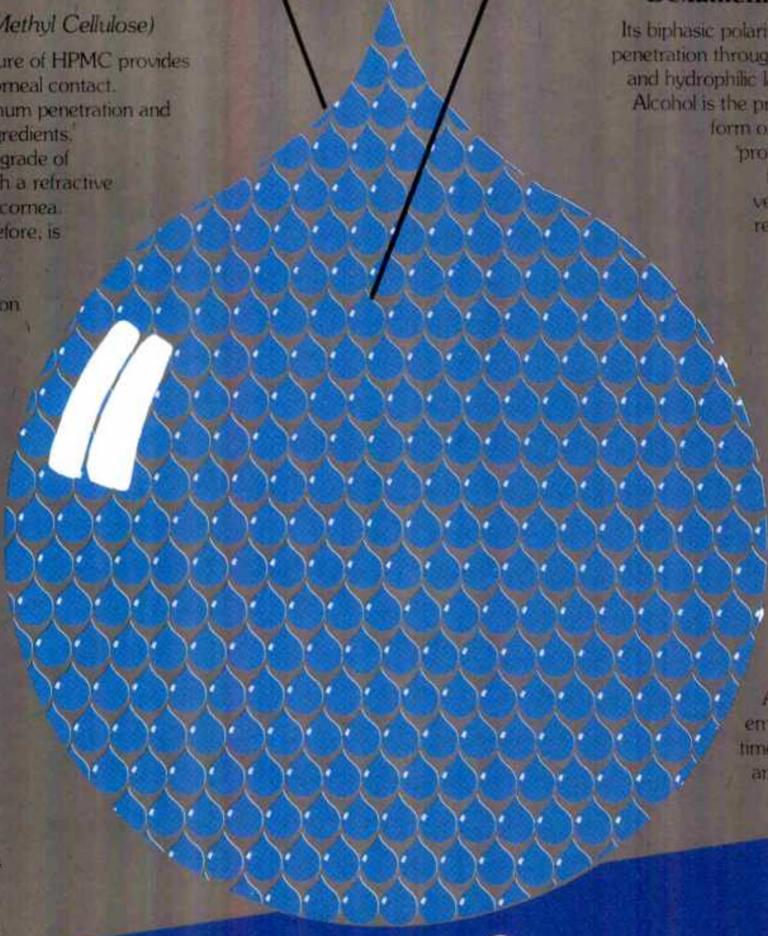

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Silicone oil keratopathy: indications for keratoplasty

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SUMMARY A penetrating corneal graft was performed in 12 patients for corneal opacification induced by silicone oil. The patients were all aphakic. They had had vitrectomy and silicone oil injection for complicated retinal detachment, often with periretinal proliferation. The average follow-up time was 13·7 months, during which four out of 11 grafts failed (one case was lost to follow-up). One patient developed severe calcific band keratopathy, and three grafts failed from endothelial decompensation. Changes induced by silicone oil include band keratopathy, thinning, and endothelial damage. The indications for keratoplasty for these corneal changes are discussed.

Silicone oil or polydimethylsiloxane fluid has been used in retinal surgery since Cibis *et al.*[1] introduced this compound in 1962. Cibis *et al.* did not find corneal changes after injection of 0·1 ml of silicone oil in the anterior chamber of the rabbit. In a clinical study of 33 patients treated with intravitreal silicone oil they noticed a central endothelial haze in two aphakic eyes where the silicone oil was in contact with the cornea. This report was followed by both animal studies[2-7] and clinical studies[8-17] describing the effects of silicone oil in contact with the endothelium. In the animal studies either no abnormalities,[2] endothelial opacification,[3] or vascularisation[5] of the cornea are mentioned. In patients treated with silicone oil band-shaped keratopathy, silicone granules in the corneal stroma, progressive vascularisation, and corneal decompensation or thinning were found.[9-18]

Corneal changes typically occur in aphakic patients when silicone oil is in permanent contact with the endothelium. In aphakic eyes without any contact of oil with the endothelium no permanent changes are reported. Occasionally emulsified oil can be seen in the superior chamber angle, occupying up to the upper third of the chamber.

Here we report on 12 patients who during 1982 underwent a penetrating corneal graft for severe corneal changes following silicone oil injection. The eyes were aphakic, and silicone oil was present in the anterior chamber and in contact with the cornea. Penetrating keratoplasty for these corneal changes has not previously been reported.

Patients and methods

During the year 1982 12 patients underwent a penetrating keratoplasty in the Rotterdam Eye Hospital for silicone oil induced corneal changes. In three patients this was a second graft. The first graft in these cases, performed during the initial reconstruction of the eye when the silicone oil was injected, became cloudy. In Table 1 the basic data for each patient are shown. The visual acuity of the affected eye before the first treatment was started and the visual acuity of the fellow eye are listed, as well as the diagnosis at the first presentation in our clinic. Most patients underwent one or more surgical interventions to treat the retinal detachment of the affected eye before silicone oil was used to support the retina. These interventions are listed in a concise form in Table 1. The visual fields of all patients except for patients 10 and 11, who could not fixate well enough, were assessed with the Goldmann perimeter before and after surgery.

OPERATIVE TECHNIQUE

The patients were treated with intraocular injection of silicone oil[19] (polydimethylsiloxane fluid) of viscosity 1000 cS, specific gravity 0·972, refractive index 1·4035, molecular weight 30 000 daltons (chain length 406 units, see Fig. 1). The keratoplasty procedure was started by baring the sclera at 10 o'clock over the pars plana. A Flieringa ring was secured to the sclera. A 6 mm to 8 mm button was trephined from the centre of the cornea, Descemet's membrane being cut with a razor blade knife or Vannas scissors. The open sky with an appropriate oil

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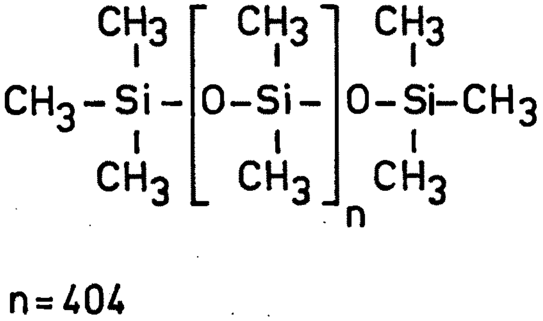
Table 1 *Pre- and postkeratoplasty data for the 12 patients under study. For each patient the sex and age as well as the visual from the first silicone oil injection to the time of grafting are given.*

Case	*Sex, age*	*VA*	*VA other*	*Diagnosis at presentation*	*No. detachment oper. before sil. inject.*	*Months to graft*	*Cornea at grafting*
1	M, 51	LP	1·0	IOFB, cataract, retinal detachment	3, incl. vitrectomy, lensectomy	7	Oedema, PCL
2	M, 33	LP	NLP	Myopia gravior, giant tear, MPP	Primary oil, lensectomy, vitrectomy, membr. peeling	11	Bullous oedema PCL
3	F, 25	NLP	NLP	Windshield perf. BE first seen in our clinic 9 mo after accident, MPP	1, incl. open sky vitrectomy and keratoplasty	18	Band kp, PCL
4	M, 67	0·1	NLP	Motorcycle accident perf. BE, aniridia, MPP	2, incl. vitrectomy membr. peeling	46	Vascularisation oedema, PCL
5	M, 41	1/60	1·0	Contusion, cataract, ECCE+IOL, detachment MPP	1, incl. buckling, SF_6 injection, laser	37	Oedema, PCL
6	M, 32	LP	NLP	Explosion, perf. BE first seen 1·5 yr after accident	Primary oil, open sky reconstruction, keratoplasty	6	Oedema, PCL
7	M, 49	LP	NLP	BE perforated 18 yr earlier (explosion)	Primary oil, vitrectomy membr. peeling	4	Oedema, PCL
8	M, 61	1/60	0.7	Myopia gravis, retinal detachment, MPP	1, incl. buckling 1st keratoplasty 22 mo after ICCE, clear 12 mo	18	Vascularisation oedema, PCL
9	M, 25	LP	1·0	Explosion, IOFB	1, incl. vitrectomy, lensectomy	34	Band kp oedema
10	M, 46	LP	NLP	Hered. macular coloboma, retinal detachment, MPP	1, incl. membr. peeling cataract extraction	22	Oedema, PCL
11	M, 72	0.5/50	0.4	ICCE+IOL, detachment, MPP	1, incl. buckling	10	Bullous kp PCL
12	F, 66	1/300	LP	ICCE, detachment BE, MPP BE	4, incl. buckling, vitrectomy, membr. peeling	22	Bullous kp

BE=both eyes. VA=visual acuity. LP=light perception. NLP=no light perception. IOFB=intraocular foreign body. IOL=intraocular lens. Visual acuity of 1/60=finger counting at 1 metre; 1/300=hand movements at 1 metre. kp=Keratopathy.

meniscus allowed the surgeon an overview of the posterior segment that had been partially hidden by the corneal opacities. By that time the decision was made whether to remove the oil from the eye or to leave the oil in the eye. In case 5 a temporary 6·5 mm Landers keratoprosthesis[20] was fixed in the 6·0 mm trephine opening to allow additional closed vitrectomy and membrane peeling to be performed. When silicone oil was to be removed, it was gently irrigated out of the open eye with balanced salt solution. When the oil had to remain in the eye because of an unstable retinal situation, the slight loss of oil during the keratoplasty was restored by oil injection through the bared scleral area at the 10 o'clock position over the pars plana. No attempt was made to separate the intraocular oil from the cornea. None of the patients had sufficient anterior chamber to be able to do so. Excised corneal buttons were cut in half and fixed in formaldehyde and glutaraldehyde for histopathological examination.



$$CH_3-\underset{CH_3}{\overset{CH_3}{Si}}-\left[O-\underset{CH_3}{\overset{CH_3}{Si}}-\right]_n O-\underset{CH_3}{\overset{CH_3}{Si}}-CH_3$$

$n=404$

Fig. 1 *Structural formula of silicone fluid (Polydimethylsiloxane, viscosity 1000 cS).*

Results

The visual acuity before and after the keratoplasty, the duration of graft clarity, and complications are listed in Table 1. We were able to assess visual fields in most patients (Fig. 2). The follow-up of these 12 patients ranged from 10 to 19 months (mean 13·7 months, SD±4·3).

acuity of the affected and the contralateral eye are listed. A short history is included in the table. The number of months elapsed

VA before	*VA after*	*Follow-up time (months)*	*Oil removed at keratoplasty*	*Months clear after keratoplasty*	*Complications and comments*
4/60	0·1	19	Yes	19	2 months following graft elevated IOP. Timolol regulated
0·5/60	5/300	18	—	18	Delayed epithelialisation. Elevated IOP. Timolol regulated
LP	LP	17	—	17	Slight band kp in the graft
1/300	2/300	7	Yes	7	After 7 months lost to follow-up Had carcinoma of the bladder
1/60	1/60	6	—	2	Abstained, see text
1/300	2/300	13	—	13	After corneal graft twice membr. peeling
LP	1/300	12	—	½(3)	Regraft after 3 weeks, see text: second graft clear for three months
1/300	4/300	13	—	13	Loose suture tightened, 5 months after keratoplasty
1/300	0.5/60	12	—	12	Slight back up, beginning after 2 months
LP	1/300	10	Yes	10	Clear
0·5/60	1/60	18	—	11	Early band kp in graft, PCL, normal thickness
1/300	2/60	6	—	6	Regrafted after 6 months, band kp and oedema

ICCE=intracapsular cataract extraction (ECCE=extracapsular). PCL=posterior collagenous layer. MPP=massive periretinal proliferation.

In three patients a slight band-shaped keratopathy developed in the graft (see Table 1, patients 3, 9, and 12) after 2 to 6 months. In a fourth patient (No. 11) a more severe band keratopathy caused a loss of transparency of the graft after 11 months. Three out of 12 grafts failed within the observation period. In two cases a regraft was performed: No. 7 after three weeks (see below) and No. 12 after six months. Case 5 had promising results from the detachment surgery, and the visual field after keratoplasty was excellent (Fig. 2). But a recurrence of periretinal fibrosis set in, and the graft became oedematous two months after grafting. The bad prognosis for retinal repair and the good visual acuity in the other eye made us abstain from further treatment. Two grafts showed delayed epithelialisation. A bandage lens overcame this problem in one case. An absolute lack of epithelial growth in patient 7, who lived abroad and could not be checked every week or so, made us perform a regraft after three weeks with a fresh donor button with viable epithelium on it.

In summary, seven out of 11 (case 4 was lost to follow-up after seven months) grafts maintained useful transparency throughout the observation period. Wound healing was not delayed or otherwise abnormal. Histology of excised keratoplasty buttons did not show any inclusions of silicone into the tissue. No homograft reactions were noted in these patients after keratoplasty.

Discussion

Permanent contact of silicone oil with the cornea results in corneal changes of various degrees of severity. A small bubble of silicone oil mobile in the anterior chamber of a phakic eye will not result in any changes of the cornea (Fig. 3, 1–6). Although emulsified oil is sometimes seen superiorly in the angle, pressure rises were not a major problem in our patients (see Table 1, complications).

Aphakic eyes that underwent complete vitrectomy with open communication between anterior and posterior segment, often with distorted or absent pupillary diaphragm, allow silicone oil to bulge

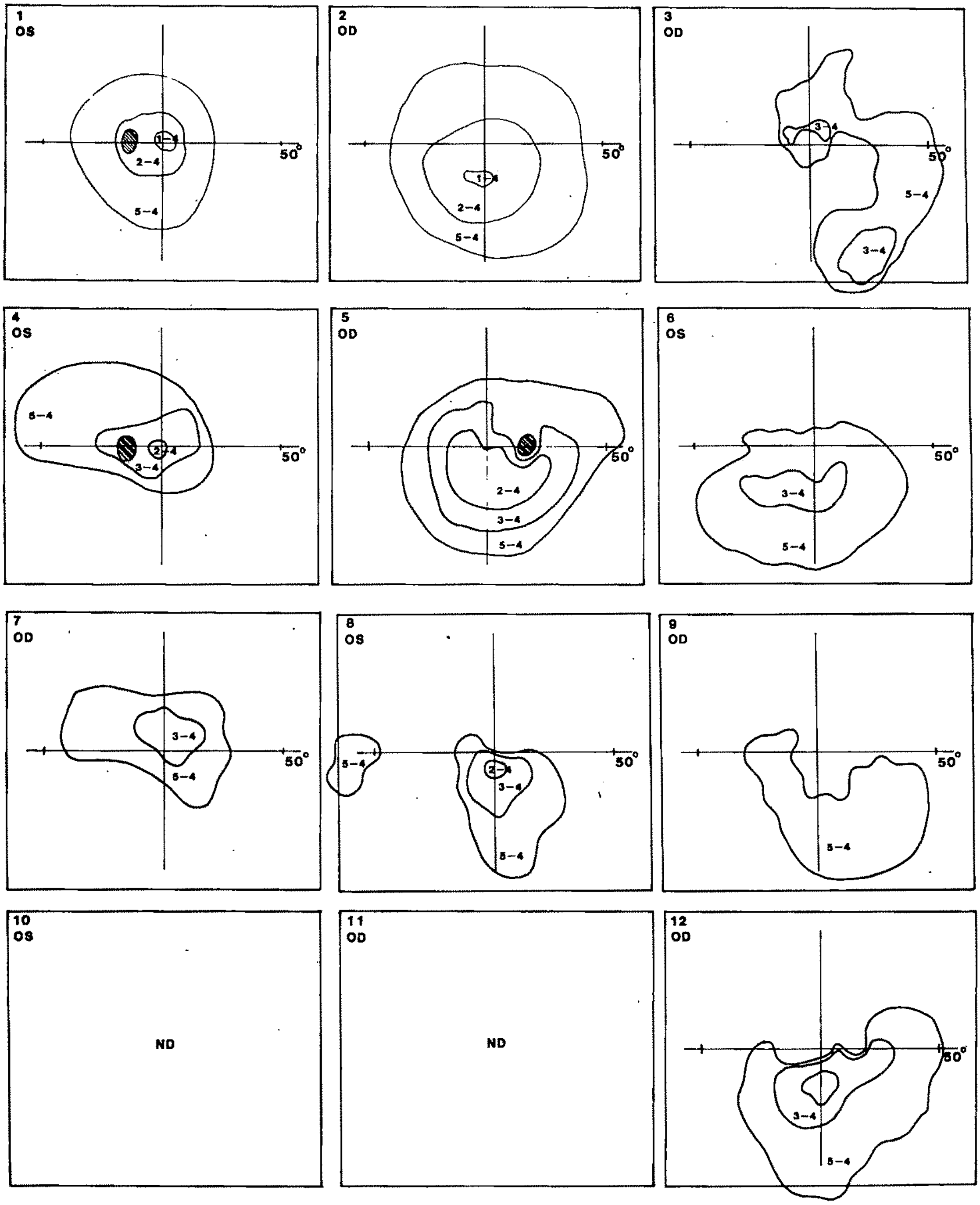


Fig. 2 *Visual field of 10 of the 12 patients, Goldmann perimetry after keratoplasty.*

forward and establish contact, either permanent or intermittent, with the endothelium (Fig. 3, 7 and 8). As the oil is lighter than the aqueous, changes in posture could change the position of the oil bubble within the eye. A silicone oil bubble in contact with the cornea at the slit lamp could very well float up a

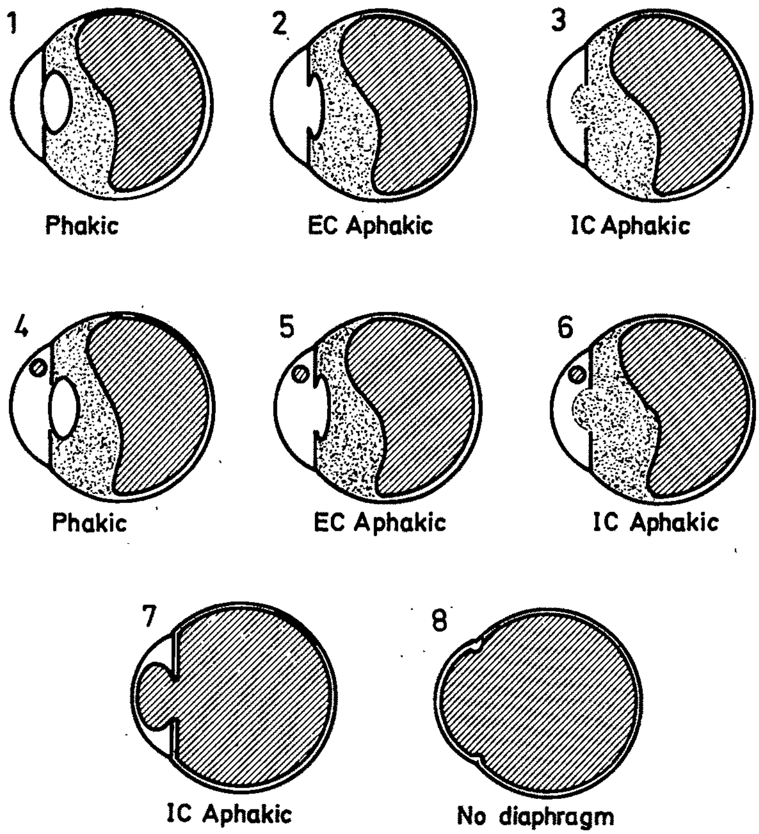


Fig. 3 *Schematic representation of the location of intraocular silicone oil. Situations 7 and 8 predispose to corneal changes.*

little and away from the cornea in a patient lying face down. Constable *et al.*[21] have suggested that higher viscosity silicone oil (12 500 cS) forms an artificial vitreous face in aphakics and has less tendency to enter the anterior chamber. Whether the higher viscosity would have the same advantage in patients with large distorted pupils or aniridia remains unanswered.

BAND KERATOPATHY

In some patients with a large silicone oil bubble in the anterior chamber a calcific band keratopathy developed (Fig. 4). The calcium salt deposits in Bowman's layer and superficial stroma[22] can be explained by a lower metabolic rate in the cornea,[23] especially in the superficial layers. Less metabolic end products like lactic acid are produced, while the loss of carbon dioxide by evaporation remains unchanged. This results in an increase in pH in the superficial corneal layers, and precipitation of calcium salts occurs. The silicone oil blocks the transport of nutrients from the aqueous into the cornea.[7] The aqueous turnover rate might be reduced. We have not made a direct measurement of aqueous turnover rate in these patients. However, we have interpreted the combined finding of a high resistance of outflow (by tonography) and a normal intraocular pressure as a support of our theory of a decreased aqueous turnover rate.

Band-shaped keratopathy alone should not be treated by keratoplasty but by chelation with disodium EDTA 2% solution after epithelial abrasion. We have undertaken lamellar grafting for this condition (as Scott suggested in 1977[18]) in one patient, but it resulted in silicone oil in the interface and a new band keratopathy in the new graft.

CORNEAL THINNING

Thinning of the cornea over silicone oil in the anterior chamber either with or without band keratopathy is frequently seen early after oil injection. It is the result of evaporation at the corneal surface while the passive leak is being occluded by the oil bubble. This mechanism was therapeutically used in the experimental treatment of bullous keratopathy by Martola and Dohlman.[4] We have performed pachometry in our patients and frequently found values below 0·45 mm central corneal thickness.

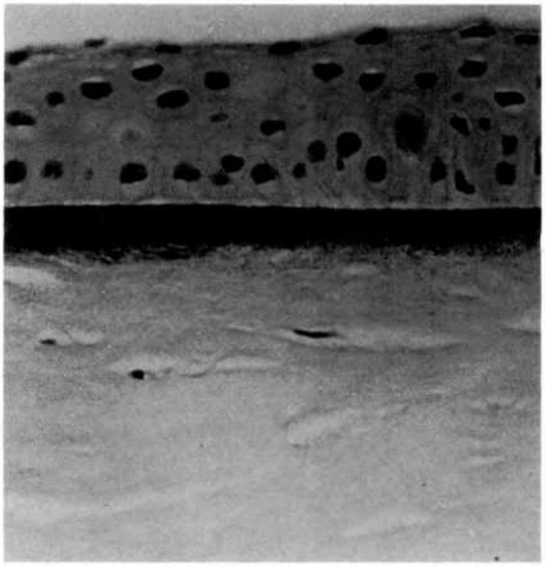


Fig. 4 *Excised corneal button, showing calcific band keratopathy at the level of Bowman's and superficial stromal layers (H and E, ×435). Courtesy of W A Manschot.*

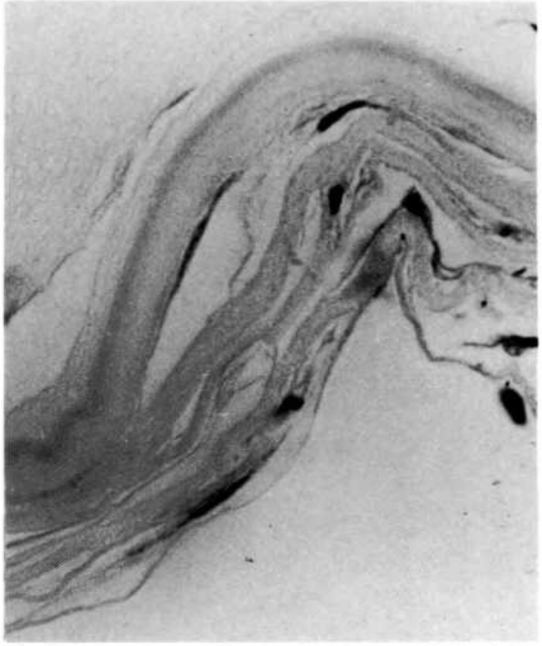


Fig. 5 *Excised corneal button, showing metaplasia of the endothelium to a posterior collagenous layer. Multilayered connective tissue interposed with fibrocytes overlies Descemet's membrane (H and E, ×435). Courtesy of W A Manschot.*

ENDOTHELIAL CHANGES

Permanent contact of oil with the endothelium of longer standing (six months or longer) results in metaplasia of endothelial cells to a posterior collagenous layer.[24] Biomicroscopically the endothelium is changed into a continuous grey layer. Specular microscopy would be an ideal way to monitor the slowly progressive endothelial transformation. Since the refractive indices of the corneal stroma and silicone oil are almost identical, there is no distinct specular reflex from the endothelial surface. Even when the endothelium is changed in a fibrous layer, the cornea may stay clear and of normal thickness so long as there is no aqueous leak into the stroma. In our experience removal of silicone oil from the eye in this situation led to corneal decompensation. The silicone oil prevents swelling of the cornea, but as soon as the oil is removed the malfunctioning endothelium will allow aqueous to leak into the stroma. In cases where silicone oil covers only the superior two-thirds of the cornea in the erect patient fluid will leak through damaged endothelium at the lower edge of the oil bubble. Eventually, however, a number of cases end in a swollen cornea and a fibrous layer facing the anterior chamber (Fig. 5).

INDICATIONS FOR KERATOPLASTY

A penetrating corneal graft in these patients does not produce the improvement in visual acuity encountered in most other keratoplasty cases. In these patients with severe retinal problems one cannot do better than at least strive for clear media, improving their visual field and clarity of vision, if not acuity of vision. Keratoplasty may also be considered when the cornea becomes too cloudy to permit funduscopy to monitor the retinal attachment or periretinal proliferative processes. To abstain from performing a graft in these patients when the cornea has become oedematous and opacified means to abstain from any further surgery, and such an eye can be considered lost. In monocular patients such a decision is very hard if not impossible to make. The corneal surgeon will always try to persuade his retinal counterpart to postpone a keratoplasty until the silicone oil can be safely removed from the eye at the time of grafting. From the above experiences with this new indication for keratoplasty we are being increasingly reluctant to perform a graft for silicone induced changes in patients with 20/40 or better vision in the other eye unless we are convinced that the chances for visual improvement are very good and the silicone oil can safely be removed from the eye.

References

1 Cibis A, Becker B, Okun E, Canaan S. The use of liquid silicone in retinal detachment surgery. *Arch Ophthalmol* 1962; **68:** 590–9.

2 Armaly MF. Ocular tolerance to silicones. *Arch Ophthalmol* 1962; **68:** 390–5.

3 Levine AM, Ellis RA. Intraocular liquid silicone implants. *Am J Ophthalmol* 1963; **55:** 939–42.

4 Martola EL, Dohlman CH. Silicone oil in the anterior chamber of the eye. *Acta Ophthalmol (Kbh)* 1963; **41:** 75–9.

5 Levenson DS, Stocker FW, Giorgiade NG. Intracorneal silicone fluid. *Arch Ophthalmol* 1965; **73:** 90–3.

6 Liesenhoff H, Schmitt J. Komplikationen durch flüssiges Silikon in der Vorderkammer. *Ber Dtsch Ophthalmol Ges* 1969; **69:** 643–4.

7 Reim M, Schütte E, Cattepoel H. Experimentelle Variation der Spiegel einiger Metabolite in der Cornea. *Ber Dtsch Ophthalmol Ges* 1971; **71:** 84–7.

8 Watzke RC. Silicone retinopiesis for retinal detachment. *Arch Ophthalmol* 1967; **77:** 185–96.

9 Cockerham WD, Schepens CL, Freeman HM. Silicone injection in retinal detachment. *Arch Ophthalmol* 1970; **83:** 704–12.

10 Blodi FC. Injection and impregnation of liquid silicone into ocular tissues. *Am J Ophthalmol* 1971; **71:** 1044–51.

11 Sugar HS, Okamura ID. Ocular findings six years after silicone injection. *Arch Ophthalmol* 1976; **94:** 612–5.

12 Manschot WA. Intravitreal silicone injection. *Adv Ophthalmol* 1978; **36:** 197–207.

13 Leaver PK, Grey HB, Garner A. Silicone injection in the treatment of massive preretinal retraction. II. Late complications in 93 eyes. *Br J Ophthalmol* 1979; **63:** 361–7.

14 Haut J, Chermet M, Van Effenterre G, Robert P. Techniques et résultats de l'injection de silicone liquide combinée à la vitrectomie dans le traitement des inversions rétiniennes. Bull Soc Ophtalmol France 1980; **80:** 517–8.

15 Haut, J, Ullern M, Chermet M, Van Effenterre G. Complications des injections intra-oculaires de silicone. *Bull Soc Ophtalmol Fr* 1980; **80:** 519–23.

16 Haut J, Ullern M, Chermet M, Van Effenterre G. Complications of intraocular injections of silicone combined with vitrectomy. *Ophthalmologica* 1980; **180:** 29–35.

17 Gonvers M. Temporary use of intraocular silicone oil in the treatment of detachment with massive periretinal proliferation. *Ophthalmologica* 1982; **184:** 210–8.

18 Scott JD. A rationale for the use of liquid silicone. *Trans Ophthalmol Soc UK* 1977; **97:** 235–7.

19 Živojnović R. Mertens DAE, Peperkamp E. Das flüssige Silikon in der Amotiochirurgie (II). Bericht über 280 Fälle, weitere Entwicklung der Technik. *Klin Monatsbl Augenheilkd* 1982; **181:** 444–52.

20 Landers MB, Foulks GN, Landers DM. Temporary keratoprosthesis for use during pars plana vitrectomy. *Am J Ophthalmol* 1981; **91:** 615–9.

21 Constable I, Mohamed S, Tan PL. Super viscous silicone liquid in retinal surgery. *Aust J Ophthalmol* 1982; **10:** 5–11.

22 Pouliquen Y, Haye C, Bisson J, Offret G. Ultrastructure de la kératopathie en bandelette. *Arch Ophtalmol (Paris)* 1967; **27:** 149–58.

23 O'Connor GR. Calcific band keratopathy. *Trans Am Ophthalmol Soc* 1972; **70:** 58–81.

24 Waring GO, Bourne WM, Edelhauser HF, Kenyon KR. The corneal endothelium. Normal and pathologic structure and function. *Ophthalmology* 1982; **89:** 531–90.

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Electroretinographic studies following vitrectomy and intraocular silicone oil injection*

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SUMMARY Vitrectomy was performed bilaterally in pigmented rabbits and followed by silicone oil injection in one eye only. Electroretinographic studies were performed preoperatively and at selected postoperative intervals. In the early postoperative period both eyes showed an initial reduction in a and b wave amplitudes, followed by a return to baseline values. The amplitudes were symmetrically and equally affected. Sequential studies over a 20-month period showed no deterioration in electroretinographic response in eyes with and without silicone oil injection.

Silicone oil injection into the vitreous cavity in the management of complicated retinal detachment was introduced in the United States by Cibis in 1961.[1 2] Numerous early laboratory studies indicated that the eye tolerated silicone oil well.[3–6] Despite initial clinical enthusiasm a high rate of failure and complication was subsequently reported in human eyes.[7] Cataract, glaucoma, and keratopathy can be major anterior segment problems after silicone oil injection.[7 8] Of more importance potentially was the suggestion in a series of animal experiments that silicone oil causes a form of retinopathy marked by early and lasting reduction in electroretinographic (ERG) amplitude, accompanied by retinal degeneration.[9–11] A decline in ERG amplitude may be due, however, to the insulating properties of the silicone oil.

While falling into disuse in the United States, the technique of silicone oil injection was further refined and advanced by Scott in England.[12–15] Encouraging results were also reported by Okun,[16 17] Grey and Leaver,[18] and Zivonjnovic and associates.[19] Anterior segment complications appeared to be important in subsequent visual loss in studies by Leaver and Grey,[8] but these difficulties are conceivably preventable by removal of the silicone oil. The question of the existence of a silicone oil retinopathy remains critical. Recent studies have demonstrated no significant decline in postoperative electroretinographic responses in the first several weeks after silicone oil injection into the vitrectomised rabbit eye.[20 21] This study extends these observations over a significantly longer period.

Materials and methods

Thirteen New Zealand pigmented rabbits weighing 3·0 to 4·0 kg were studied. One to two weeks before the start of the experiments five to eight cryotherapy applications were placed in the nasal retina to produce an area of chorioretinal adhesion through which an incision could be made for insertion of the vitrectomy instrument.[22] General anaesthesia consisted of intramuscular injections of ketamine 1·0–2·0 ml and acepromazine 1–2 mg/kg for all operative procedures.

Preoperatively and one to two weeks later electroretinograms were recorded. Photic stimulation was supplied by a Grass PS-22 photostimulator with the flash unit placed perpendicular to the visual axis and 6 inches (15 cm) from each eye. Responses were sensed by a bipolar corneal electrode of conventional design (Burian Allen), differentially amplified (Tektronix 7A22; 3 db points (points beyond which 50% of the signal was attenuated to reduce noise within the system): 0·1300 Hz), and displayed on the face of a storage oscilloscope (Tektronix 7313).

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The rabbits were kept in the darkened test room for at least 30 minutes prior to evaluation. Recordings were made with the rabbits held in a special plastic restraining box. The eyes were topically anaesthetised with a 0·5% solution of proparacaine hydrochloride prior to insertion of the corneal electrode; otherwise the rabbits remained unmedicated throughout the recording session.

Each eye was evaluated at two flash radiances: maximum photostimulator radiance (I 16) and approximately one-quarter maximum (I 4). All electroretinographic data presented are based on the averages of two responses at each flash radiance.

Under repeat anaesthesia a vitrectomy was performed bilaterally on the same day in 12 rabbits. In the 13th animal surgery was performed in one eye only. In addition to intramuscular ketamine and acepromazine 1 ml of lignocaine 1% was injected retrobulbarly for each eye. Pupils were dilated prior to surgery with cyclopentolate 1% and phenylephrine hydrochloride 10%, two drops each to each eye.

Initial incisions were carried through previously treated inferonasal retina with a sclerotome. The Machemer vitreous infusion suction cutter (VISC) with light source was placed through the incision and a pre-placed 5–0 Mersilene suture tied around it to render the incision water tight. Ringer's lactate infusion was used in all eyes. An attempt was made to remove as much vitreous gel as possible; to this end a tiny drop of fluorescein was injected into many eyes to provide greater demarcation of the gel. All surgery was performed under microscopic control.

Silicone oil was injected into only one eye of the two operated eyes using a 16 gauge cannula; the fellow operated eye served as a control. Medical grade silicone oil of 1000 centistokes viscosity, supplied through the courtesy of Mr Peter Leaver and Dr Robert Machemer, was used in all cases. The amount injected varied from 1·0 to 1·9 ml, producing an estimated fill of the vitreous cavity of 60–90%. In most cases approximately 80–90% of the vitreous cavity appeared to be filled with silicone oil. Postoperative clinical examinations and sequential electroretinograms were recorded from day one postoperatively and continued at selected intervals for 20 months.

One eye with silicone oil injection developed a retinal detachment after one month; the fellow eye was followed up for two months. One eye undergoing vitrectomy alone developed a retinal detachment three months after surgery; the fellow eye was followed up for nine months.

Histological examinations of both eyes were performed at the following time intervals: four days (1); two months (1); three months (1); six months (2); nine months (1). To obtain the specimens the animals were deeply anaesthetised, and their eyes were enucleated; they were then immediately killed. Immediately after enucleation the eyes were placed in a fixative consisting of 1% glutaraldehyde, 1% formaldehyde in 0·1 M phosphate buffer, pH 7·0–7·2, at room temperature (20°C). After one minute an incision approximately 1 cm in length was made along the pars plana to facilitate penetration of fixative. One hour later the anterior segment was removed, and the tissue was allowed to fix overnight at 4°C. Finally the tissue was washed in buffer, dehydrated, and embedded in epoxy resin. Semithin sections (1 µm) were cut on a DuPont Sorvall Porter Blum MT-2B ultramicrotome, mounted on glass slides, and stained with toluidine blue for light microscopy.

Results

The average preoperative b wave value was 161 microvolts for eyes undergoing vitrectomy alone and 170 microvolts for eyes subjected to vitrectomy and silicone oil injection (Table 1). Two days postoperatively there was equal and symmetrical decrease in b wave amplitudes in both sets of eyes (Table 1 and Fig. 1). Eyes undergoing vitrectomy alone decreased 31% (ΔB=−50 microvolts); eyes with vitrectomy and silicone oil injection declined 39% (ΔB=−67 micro-

Table 1 *b wave amplitude (microvolts)*

	Vitrectomy		*Vitrectomy+silicone oil*	
	No. of animals	*Avg. value ± SE*	*No. of animals*	*Avg. value ± SE*
Preoperative	12	161±9·6	13	169±13·2
Postoperative				
Day 2	5	116±17·8	6	113±16
5	5	166±31·7	6	122±21
14	7	191±16·3	7	233±27
30	4	258±34	3	223±121
Month 2	7	188±16·7	8	188±21·2
3	6	213±26	7	201±14
6	4	176±39	6	160±14

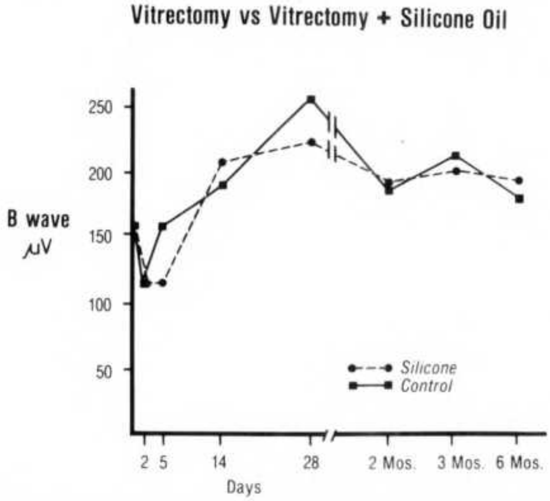

Fig. 1 *b Wave amplitudes are plotted against postoperative time.*

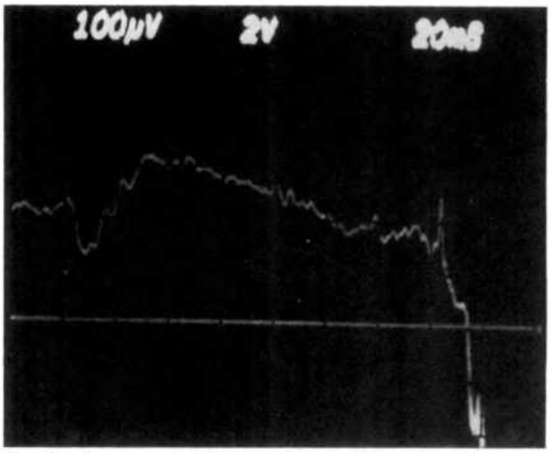

Fig. 3 *Preoperative electroretinographic tracings from an eye undergoing vitrectomy alone (control).*

volts) (Fig. 2). By the seventh postoperative day eyes with vitrectomy alone showed a rise in b wave amplitude of 25% (ΔB=41 microvolts) over baseline values (Figs. 3–8). Eyes undergoing vitrectomy and silicone oil injection rose 35% (ΔB=60 microvolts) compared with baseline preoperative values. Values in both groups of eyes tended to remain slightly above baseline for a six-month period of observation, showing a slow shift back to near baseline. In some eyes the increases in the first postoperative week were as much as 100% of baseline values.

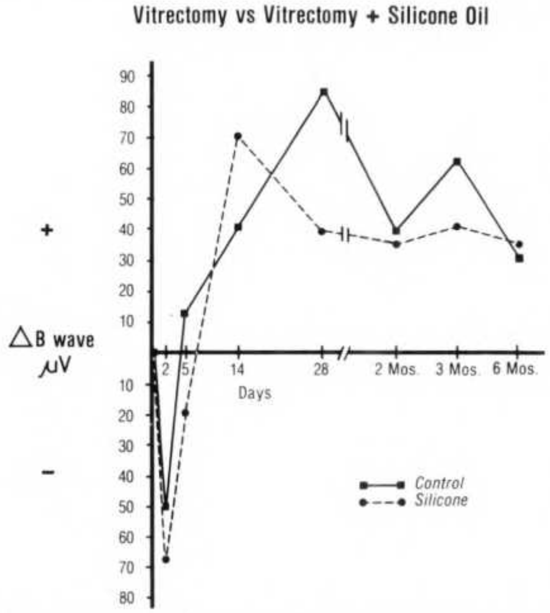

Fig. 2 *Changes in b wave amplitudes are plotted against postoperative time.*

Nine months postoperatively one eye undergoing vitrectomy alone showed a fall from a baseline value of 180 to 130 microvolts (ΔB=−50 microvolts); three eyes undergoing vitrectomy and silicone oil injection at the same time showed an average fall from baseline values of 13 microvolts (ΔB=−13).

Three animals were retested on a different flash unit and amplifier at 14 months, 17 months, and 20 months postoperatively. Comparisons are valid only between eyes of the same animal and not compared with control values because of the change in equipment. In the animal tested 14 months postoperatively the b wave values at 116 were: vitrectomy alone, 140 µv, vitrectomy and silicone oil injection, 185 µv. In the animal studied 17 months postoperatively one eye had no operation (B=80 µv); the fellow eye had undergone vitrectomy and silicone oil injection (B=80 µv). In the animal studied 20 months post-

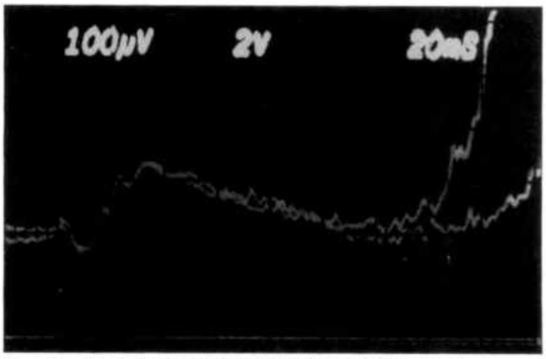

Fig. 4 *Four-day postoperative electroretinographic tracings from control eye in Fig. 3.*

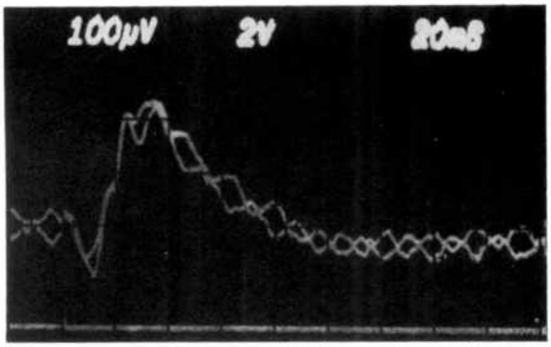

Fig. 5 *Four-week postoperative electroretinographic tracings from control eye in Fig. 3.*

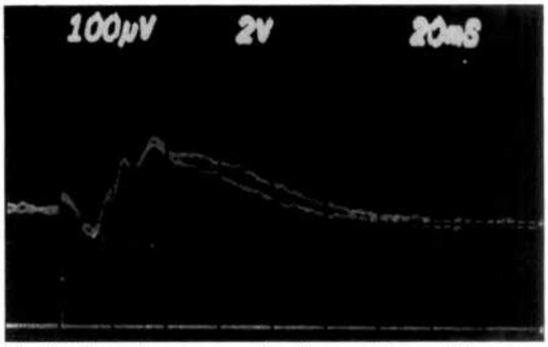

Fig. 7 *Four-day postoperative electroretinographic tracings from fellow eye in Fig. 6.*

operatively, b wave values were: vitrectomy alone, 90 μv, vitrectomy and silicone oil injection, 100 μv.

Studies of histology by light microscopy showed no alteration of normal retinal pigment epithelium architecture in either control or silicone injected eyes four days after surgery. In the specimen studied two months postoperatively an eye without silicone injection was found to be largely without abnormalities, except for one section, which showed a focal area of photoreceptor loss and outer nuclear layer loss. The fellow eye had cataract and retinal detachment.

In specimens studied three months postoperatively the eye undergoing vitrectomy showed no alterations, while that having undergone silicone injection showed only a few lipid droplets at the level of the retinal pigment epithelium without any disruption of retinal architecture (Fig. 9).

Six months postoperatively one animal showed no abnormalities in either eye. In a second animal the control eye had occasional pyknotic nuclei in the photoreceptor layer resembling late stages of photic damage. Other eyes had some loss of outer and inner segments, intraretinal macrophages, and mild metaplasia of the retinal pigment epithelial cells. Most areas remained normal. In the eye with silicone injection the superior retina and visual streak appeared normal. There was one hypopigmented area, however, which showed loss of outer segments and invasion of the retina by pigmented macrophages. The retinal pigment epithelium tended to be bunched together in this area, together with an increase in the pigment content of the cells (Fig. 10).

In the animal killed nine months postoperatively the control eye had developed a retinal detachment, and there was a prominent loss of photoreceptors. The eye containing silicone was normal, except for a slight random increase in pigmentation in the retinal pigment epithelium in some areas of the superior retina. Despite inability to remove cortical vitreous in the rabbit, essentially no vitreous was histologically detectable in superior areas of the retina where silicone oil had been in constant contact with the retinal surface in any of the specimens.

Discussion

Surgical intervention into the vitreous cavity produces a fall in the amplitude of both a and b waves

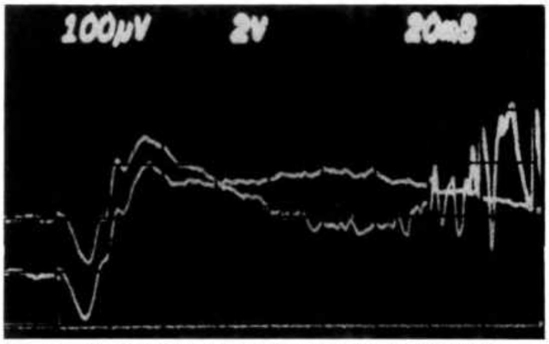

Fig. 6 *Preoperative electroretinographic tracings from fellow eye undergoing vitrectomy and silicone oil injections.*

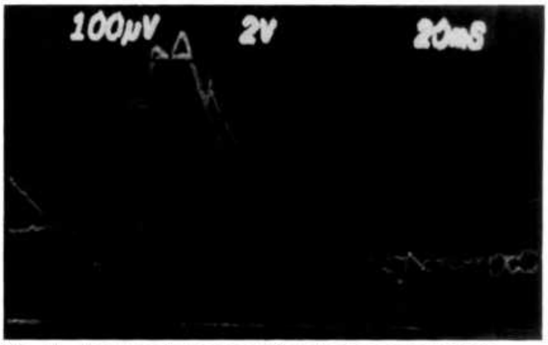

Fig. 8 *Four-week postoperative electroretinographic tracings from fellow eye in Fig. 6.*

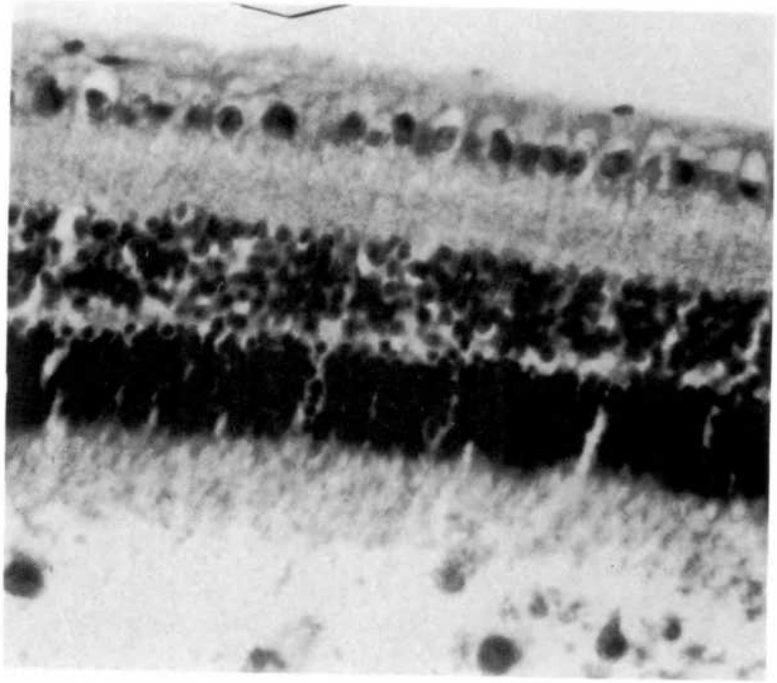

Fig. 9 *Retina maintains normal architecture three months after vitrectomy and silicone oil injection without evidence of residual vitreous. (Haematoxylin and eosin, ×125).*

of the electroretinogram,[23 24] a finding confirmed by the control eyes in our study. On day 2 eyes with vitrectomy alone showed a decrease of 31% of b wave amplitude, while those with vitrectomy and silicone oil injection showed an average decline of 39%, comparable with results after surgical injury alone reported by Declerq and colleagues.[23] The degree of initial decline has been found in part to vary with

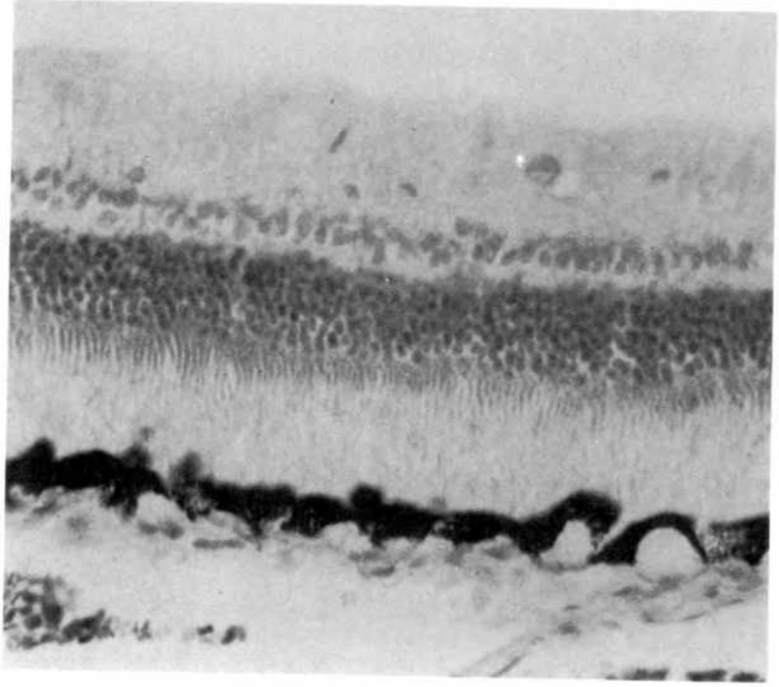

Fig. 10 *Retina maintains normal architecture six months after vitrectomy and silicone oil injection without evidence of residual vitreous on retinal surface. (Luxol fast blue, ×125).*

surgical irrigating solution,[24] though decreases in b wave amplitude may occur with scleral puncture alone without intraocular irrigations.[23]

Eyes with and without silicone showed equal and parallel initial declines in b wave amplitudes, followed by increases to levels greater than baseline values. The initial decline can now be attributed to surgical intervention alone rather than to an effect of silicone in the vitreous cavity, as previously concluded.[9]

With surgical intervention alone,[23 24] or with silicone implantation, ERG a and b wave values usually return to normal between two and seven days after surgery. Armaly[5] has also previously demonstrated normal ERGs after prolonged implantations of silicone in the vitreous cavity. Prolonged reduction or increasing loss of amplitude may be produced by implanting a metallic foreign body in the vitreous cavity or by injecting blood.[25]

The increase in b wave amplitude to values greater than normal has not been previously reported and is not readily explained. In experimental models a and b wave amplitudes may be increased by lowering temperature and increasing pH.[26] Alterations in ionic content of the solution bathing the retina may also produce alterations in wave forms.[26 27] Such local changes may occur in vitrectomised eyes but have not been systematically correlated with electroretinographic changes. Increases in vitreous calcium, magnesium, and protein concentration occur after vitrectomy, while vitreous potassium is decreased.[28] These changes usually revert to normal, however, more quickly than does the increased b wave amplitude we noted.

Lee and associates[9] demonstrated early histological changes in rabbits and monkeys consisting of swelling in the nerve fibre layer and hydropic vacuolisation of ganglion cells in the retina. There were early cloudy swelling changes in the rods and cones. These findings reverted to normal in the late stages, leaving only a reduction in the ganglion cells and a commensurate reduction of the thickness of the ganglion cell layer. Although these latter changes were noted to be associated with a suppressed ERG, the ganglion cell layer is not thought to make any contribution to the ERG; therefore there cannot be a causal relationship between these two findings.

Mukai and colleagues[10] noted spaces within the retina shortly after silicone injection, which he interpreted as silicone particles. Phospholipids were noted at the vitreoretinal interface. Later studies identified empty spaces in the inner segment of the retina.[11]

Our findings of little change in the histology on light microscopy confirm earlier work by Armaly[5] and LaBelle and Okun.[6] Neither of these previous investigations demonstrated long-term damage to the retina by intravitreal silicone oil. Early retinal oedema was noted in both control and silicone injected eyes by LaBelle and Okun[6] and was attributed to surgical trauma.

Pathological studies in man after silicone oil injection are limited.[29-33] One detailed study by Manschot[29] demonstrated degeneration in a retina that was chronically detached, while two additional studies[30 31] noted changes in eyes which had been phthisical for five years. Studies on an eye which had been phthisical for only a few months[8] showed only a few vacuoles within the nerve fibre layer, with a homogeneous layer of moderate electron density overlying the inner limiting membrane. The intraretinal globules were contained within macrophages and glial cells rather than affecting the neurosensory elements of the retina. Okun[17] noted that studies of 13 eyes studied pathologically after silicone oil injection showed only minimal reaction to the silicone itself, but these cases were not recorded in detail.

No evidence of clinical silicone retinopathy has ever been demonstrated.[7 8 16 17 31] On the contrary, long-term follow-up studies have demonstrated maintenance of vision for three,[18] 10,[14] and 12[17] years once the retina is reattached without evidence of loss of vision attributable to silicone toxicity. The absence of significant decline in the electroretinographic response from animal eyes undergoing vitrectomy and silicone oil injection supports the concept that the retina tolerates intraocular silicone well and does not provide evidence for a functional silicone retinopathy.

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References

1 Cibis PA, Becker B, Okun E, Canaan S. The use of liquid silicone in retinal detachment surgery. *Arch Ophthalmol* 1963; **68:** 590–9.

2 Cibis PA. Vitreous transfer and silicone injections. *Trans Am Acad Ophthalmol Otolaryngol* 1964; **68:** 983–7.

3 Stone W Jr. Alloplasty in surgery of the eye. *N Engl J Med* 1958; **258:** 486–502.

4 Levine AM, Ellis RA. Intraocular liquid silicone implants. *Am J Ophthalmol* 1963; **55:** 939–43.

5 Armaly MF. Ocular tolerance to silicones. I. Replacement of aqueous and vitreous by silicone fluids. *Arch Ophthalmol* 1962; **68:** 390–5.

6 LaBelle P, Okun E. Ocular tolerance to liquid silicone: an experimental study. *Am J Ophthalmol* 1972; **7:** 199–204.

7 Watzke RC. Silicone retinopoiesis for retinal detachment. *Arch Ophthalmol* 1967; **77:** 185–96.

8 Leaver PK, Grey RHB, Garner A. Silicone oil injection in the treatment of massive periretinal proliferation. II. Complications in 93 eyes. *Br J Ophthalmol* 1979; **63:** 361–7.

9 Lee P, Donovan RH, Mukai N, Schepens CL, Freeman HM. Intravitreous injection of silicone: an experimental study. I. Clinical picture and histology of the eye. *Ann Ophthalmol* 1969; **1:** 15–25.

10 Mukai N, Lee P, Schepens CL. Intravitreous injection of silicone: an experimental study. II. Histochemistry and electron microscopy. *Ann Ophthalmol* 1972; **4:** 273–87.

11 Mukai N, Lee P, Oguri M, Schepens CL. A long term evaluation of silicone retinopathy in monkeys. *Can J Ophthalmol* 1975; **10:** 391–402.

12 Scott JD. The treatment of massive vitreous retraction by separation of preretinal membranes using liquid silicone. *Mod Probl Ophthalmol* 1975; **15:** 285–90.

13 Scott JD. Equatorial giant tears affected by massive vitreous retraction. *Trans Ophthalmol Soc UK* 1976; **96:** 309–12.

14 Scott JD. A rationale for the use of liquid silicone. *Trans Ophthalmol Soc UK* 1977; **97:** 235–7.

15 Scott JD. A rationale for the use of liquid silicone in retinal detachment surgery. In: Shimuzu K, ed. *International Congress Series 450 XXII Concilium Ophthalmologicum, Kyoto.* Amsterdam-Oxford: Excerpta Medica, 1978.

16 Okun E. Intravitreal surgery utilizing liquid silicone. A long term follow up. *Trans Pac Coast Otoophthalmol Soc* 1968; **49:** 141–59.

17 Okun E. The current status of silicone oil (analysis of long term successes). In: Irvine AR, O'Malley C, eds. *Advances in vitreous surgery.* Springfield: Thomas, 1976: 518–22.

18 Grey RHB, Leaver PK. Silicone oil in the treatment of massive periretinal proliferation. I. Results in 105 eyes. *Br J Ophthalmol* 1979; **63:** 355–60.

19 Zivonjnovic R, Mertens DAE, Baavsma GS. Das flüssige Silikon in der Amotiochirurgie. *Klin Monatsbl Augenheilkd* 1981; **179:** 17–22.

20 Meredith TA, Lindsey DT, Goldman AI. Electroretinographic evaluation after vitrectomy and silicone oil injection. *Invest Ophthalmol Visual Sci* 1981; **20** (suppl): 199.

21 Ober RA, Blanks JC, Ogden TE, *et al.* Retinal tolerance to liquid silicone. *Retina* 1983; **3:** 77–85.

22 Abrams GW, Topping T, Machemer R. An improved method for practice vitrectomy. *Arch Ophthalmol* 1978; **96:** 521–5.

23 Declerq SS, Meredith CA, Rosenthal AR. Experimental siderosis in the rabbit. *Arch Ophthalmol* 1977; **95:** 1051–8.

24 Moorhead LC, Redburn DA, Merritt J, Garcia CA. The effects of intravitreal irrigation during vitrectomy on the electroretinogram. *Am J Ophthalmol* 1979; **88:** 239–45.

25 Mandelbaum S, Cleary PE, Ryan SJ, Ogden TE. Bright-flash electroretinography and vitreous hemorrhage. *Arch Ophthalmol* 1980; **98:** 1823–8.

26 Winkler BS. The electroretinogram of the isolated rat retina. *Vision Res* 1972; **12:** 1183–97.

27 Winkler BS, Simson V, Banner S. Importance of bicarbonate in retinal function. *Invest Ophthalmol Visual Sci* 1977; **16:** 766–8.

28 Killey FP, Edelhauser HG, Aaberg TA. Intraocular fluid dynamics: measurements following vitrectomy and intraocular sulfur hexafluoride. *Arch Ophthalmol* 1980; **98:** 1448–52.

29 Manschot WA. Intravitreal silicone injection. *Adv Ophthalmol* 1978; **36:** 197–207.

30 Sugar HS, Okamura ID. Ocular findings in six years after intravitreal silicone injection. *Arch Ophthalmol* 1976; **94:** 612–5.

31 Blodi FC. Injection and impregnation of liquid silicone in ocular tissues. *Am J Ophthalmol* 1971; **71:** 1044–51.

32 Watzke RC. Silicone retinopoeisis for retinal detachment: a pathologic report. *Surv Ophthalmol* 1967; **12:** 333–7.

33 Cockerham WD, Schepens CL, Freeman HM. Silicone injection in retinal detachment. *Arch Ophthalmol* 1970; **83:** 704–12.

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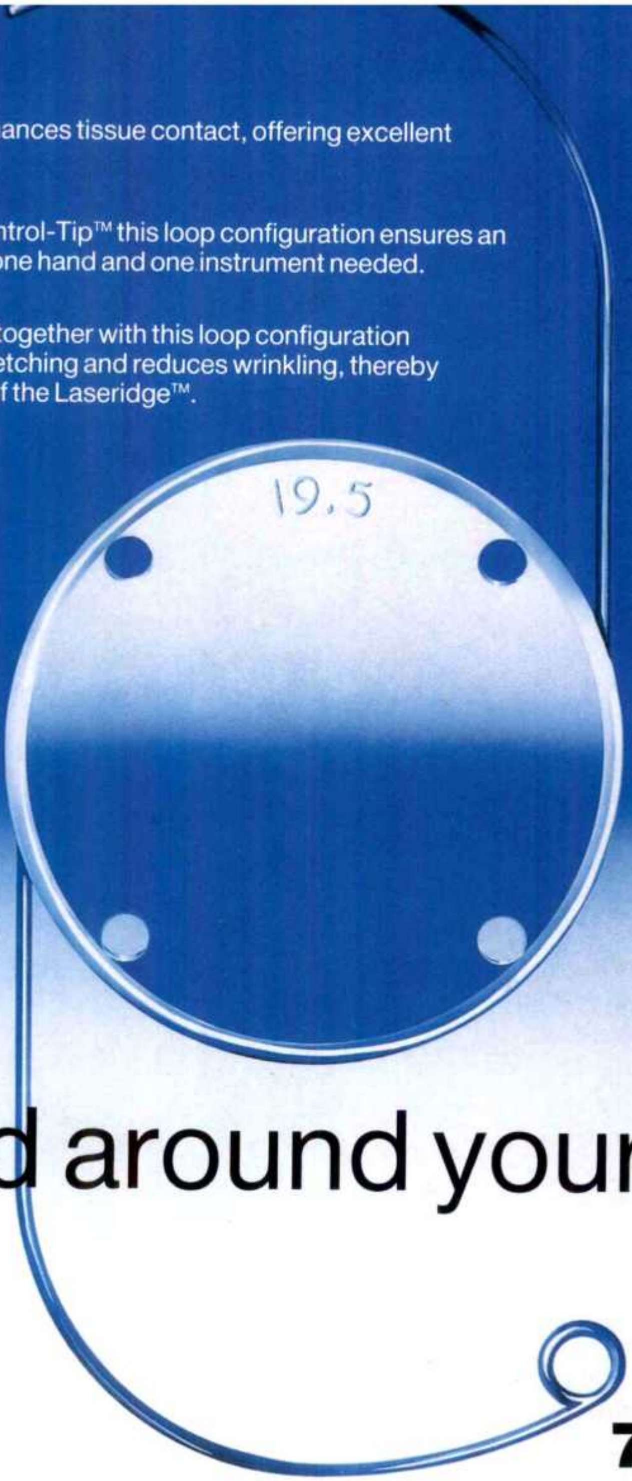

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Long-term outcome of primary acute angle-closure glaucoma

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SUMMARY Factors influencing the long-term cure of 116 consecutive cases of acute angle-closure glaucoma, with at least one year's follow-up were examined. Delay in presentation and the time needed to terminate the attack were found to have a detrimental effect on the final outcome, while the height of the intraocular pressure at the time of the attack was found to be unimportant in predicting the long-term prognosis of the disease.

It is not clear whether primary acute angle-closure glaucoma (AACG) has a favourable outcome when iridectomy is performed during the acute stage of the disease. Factors like duration of the attack have not been thoroughly investigated. A late increase in the intraocular pressure (IOP) after an apparently successful terminated attack of AACG by iridectomy has been reported.[1-5] The rate of this delayed rise in IOP is reported to be between 19%[3] and 24%.[2] The reason for it has not been elucidated. Some authors have blamed the surgical procedure of peripheral iridectomy,[1 3] while others could not report on any positive correlation between various factors and the late outcome.[4 6]

The almost unique arrangement by which our department and institute render ophthalmological services exclusively to a large population offers an excellent opportunity for long-term studies. Taking advantage of this we analysed the follow-up records over an 11-year period of all patients treated for AACG who had been followed up for at least one year after the attack, and we attempted to analyse the influence of factors prior to surgery on the late outcome of AACG.

Materials and Methods

The files of 116 consecutive patients treated in our department for AACG between 1 January 1972 and 31 December 1982 were retrieved and the following data recorded: (1) the time which elapsed between the onset of the AACG attack and the diagnosis was made and treatment started; (2) the IOP reading at the time of the diagnosis; (3) attack terminated (or not) by conventional medical therapy; (4) how long after beginning treatment the attack was terminated; (5) final outcome one year or later after the attack, namely, 'cured' with no additional medical treatment; 'not cured' needing continuous medical therapy, and/or having glaucomatous damage, and/or needing further glaucoma surgery.

All data were fed into the computer and the relationship between the various parameters analysed. Statistical significance was tested by the χ^2 method.

In this study we examined the final outcome of each case and related it to three preoperative data, namely, delay in presentation, height of the IOP during the attack, and the time needed to terminate the attack by conventional medical therapy.

Results

Delay in presentation. For 94 patients who were followed up for at least one year information was available on the time elapsing between the onset of symptoms and start of treatment. Table 1 presents

Table 1 *Relationship between presentation time and final outcome*

	Cured	*Not cured*
<24 h	45	7
≥24 h	20	22

$\chi^2=16·49$; $p<0·001$.

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Table 2 *Effect of the height of IOP at presentation on the final outcome of AACG*

IOP at presentation	*Total*	*Final outcome*			
		Cured		*Not cured*	
		n	%	*n*	%
≤40 mmHg	16	10	62·5	6	37·5
>40 mmHg	81	58	71·6	23	29·4

$\chi^2=0{\cdot}53$; $p>0{\cdot}5$.

the correlation between delay in presentation and the final outcome. Patients with less than 24 hours' delay in presentation had a more favourable outcome than those with 24 hours' delay or more. This difference between the two groups was found to be statistically significant ($p<0{\cdot}001$).

Height of the IOP during the AACG attack. The height of the IOP when the patient first presented to the emergency room or to the referring ophthalmologist had practically no effect on the final outcome (Table 2).

Time needed to terminate the attack. This information was available for just over half of the cases. Although the numbers were small, a clear correlation was apparent. The longer it took to terminate the AACG attack, the worse the long-term prognosis. Six out of seven patients who could not be relieved of their acute attack with the usual medical treatment prior to iridectomy developed glaucomatous damage and/or needed filtration surgery.

Discussion

In our department a prophylactic iridectomy was performed on all fellow eyes (surgical in the first years and laser in later years), so we could evaluate the effect of a possible surgical insult on these eyes. None of these fellow eyes developed such a late rise of IOP, and therefore, when this occurs in the AACG eye, it cannot be attributed to the procedure of iridectomy but must be due to the disease process of AACG, and it is our belief that this is connected with events prior to surgery.

The importance of the delay in presentation as seen in Table 1 indicates that patients arriving, diagnosed, and treated within 24 hours less often have a late increase in IOP than those who present later. The fact that the height of the IOP during the acute attack has no effect on the final outcome has been reported previously[4] and was confirmed in this study.

Our results also indicate the importance of the duration of the attack, as expressed both by the delay in presentation and by the time elapsing between initiation of treatment and until the termination of the attack. The longer the time between presentation and termination of the attack, the higher is the risk for a future elevation of the IOP. Analysis of the data showed that most of the cases with delayed presentation were also relieved of their attack after a longer period of time. We therefore assume that the time factor plays an important role in the formation of peripheral anterior synechiae, iris atrophy with pigment deposits in the angle, etc, factors which later interfere with the normal angle filtration.

The effect of delay in presentation was previously investigated by Hillman,[6] who did not find it to be related to the final IOP. Our study re-examined the effects of delay in presentation and the time needed to terminate the attack, and we found that this duration of the AACG attack certainly has a detrimental effect on the long term outcome of the affected eye.

Playfair and Watson[4] reported that all the changes in their patients occurred within four months after the attack. Though we examined our results at least one year later, in retrospect we can state that a careful follow-up of 6–12 months is probably sufficient in those 70–75% of cases which will be trouble-free and may be discharged from follow-up, as they can be considered cured.

References

1 Floman B, Berson D, Landau L. Peripheral iridectomy in closed-angle glaucoma—late complications. *Br J Ophthalmol* 1977; **61:** 101–4.

2 Krupin T, Mitchell KB, Johnsohn MF and Becker B. The long term effects of iridectomy for primary acute angle-closure. *Am J Ophthalmol* 1978; **86:** 506–9.

3 Saraux H, Offret H. Long-term study of patients with iridectomy for angle-closure glaucoma. *Glaucoma* 1979; **1:** 149–51.

4 Playfair TJ, Watson PG. Management of acute primary angle-closure glaucoma: a long-term follow-up of the results of peripheral iridectomy used as an initial procedure. *Br J Ophthalmol* 1979; **63:** 17–22.

5 Bobrow JC and Drews RC. Long-term results of peripheral iridectomies. *Glaucoma* 1981; **3:** 319–22.

6 Hillman JS. Acute closed-angle glaucoma: an investigation into the effect of delay in treatment. *Br J Ophthalmol* 1979; **63:** 817–21.

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Prevalence of posterior subcapsular lens opacities in patients with retinitis pigmentosa

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SUMMARY We clinically evaluated 338 patients with various genetic types of retinitis pigmentosa (RP) for the presence of posterior subscapsular (PSC) lens opacities. Of these, 180 (53%) had PSC lens changes or were bilaterally aphakic. Patients with X-linked recessive RP showed a greater prevalence and patients with autosomal dominant RP a lesser prevalence of PSC lens changes compared with autosomal recessive or isolated cases.

Previous authors have presented data or observations on cataracts in patients with retinitis pigmentosa (RP). These reports have varied from descriptions of ultrastructural changes[1 2] to advantages of cataract surgery[3] to data on the prevalence of posterior subcapsular (PSC) lens changes in RP.[4 5]

This paper records the prevalence of PSC cataract in 338 patients with various genetic types of RP and emphasises the patient's age and genetic type as relevant factors in the determination of PSC lens opacities in RP patients. These data extend and modify those from previous investigations.

Patients and methods

All patients with RP seen by one of us (G.A.F) between January 1977 and August 1982 were included in this study. Of these 338 patients 173 (51·2%) were male and 165 (48·8%) were female. Their mean age was 38·7 years, median 37 years, range 4 to 77 years. An assessment of racial distribution showed 249 (73·7%) were white, 64 (18·9%) were black, and 25 (7·4%) were Hispanic or Oriental. A determination of the genetic types demonstrated that 96 (28·4%) of the patients were autosomal dominant, 62 (18·3%) were autosomal recessive, 40 (11·8%) were X-linked recessive, and 140 (41·4%) were isolated cases.

Each patient was personally examined by one of us (G.A.F.) and was given a complete ocular examination, including an external evaluation and slit-lamp biomicroscopy of the cornea, anterior chamber, lens, and vitreous. Examination of the lens was done after the instillation of a mydriatic. Ocular pressures were checked by applanation tonometry, and the fundus was examined by both direct and indirect ophthalmoscopy. Patients were further assessed by visual field examination, electroretinography, and fundus photography. In selected cases dark adaptometry was also performed with a Goldmann-Weekers dark adaptometer.

The diagnosis of RP was based on a history of night blindness, various degrees of bilateral peripheral visual field loss, reduction or absence of rod function, and in most cases reduction or absence of cone function determined by electroretinography and fundus changes. In most cases the fundus changes included attenuated retinal vessels, variable amounts of pigment clumping with anterior migration in the form of bone spicule pigmentation, and hypopigmentation of the retinal pigment epithelium, most apparent in the midperipheral retina. 'Wax' disc atrophy was also noted, but not in all patients. We excluded patients considered to have sector, unilateral, or other 'atypical' forms of RP, such as a localised or 'delimited' type[6]; those with congenital deafness (Usher's syndrome) or with syndromes associated with RP, such as the Bassen-Kornweig syndrome, Refsum's syndrome, or the Bardet-Biedl syndrome; and patients categorised as having a cone-rod dystrophy, choroideremia, or gyrate atrophy of the choroid and retina. A review of family pedigrees facilitated the classification of patients with specific genetic types based on criteria for categorisation previously described.[7]

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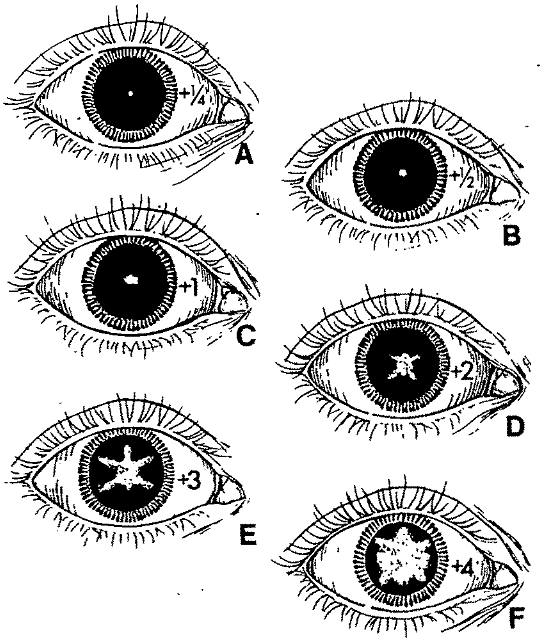

Fig. 1 *Clinical grading system used to quantitate the degree of posterior subcapsular (PSC) lens opacities.*

The presence of PSC cataracts was determined by one of us (G.A.F) with the aid of a slit-lamp biomicroscope. An attempt was made to quantitate the degree of lens alteration by an arbitrary grading system of +¼ to +4 (Fig. 1). For the purpose of analysis bilaterally aphakic patients were included among those having a cataract (17 patients). Mild opacities were considered as ≤+1, moderate as +2, and marked as ≥+3. Asymmetry in lens changes between eyes was occasionally apparent. In 13 patients the PSC changes were exclusively monocular. Although the development of anterior subcapsular opacities would also appear to be associated with the presence of RP, their incidence is considerably less than that of PSC lens changes, and so they were not recorded in our series of patients.

Results

Table 1 *Distribution of subjects, age, and genetic group*

Age group (yr)	Dominant	X-linked	Isolated	Recessive
0–9	3	5	1	2
10–19	5	12	15	4
20–29	27	9	28	11
30–39	17	6	26	10
40–49	10	4	25	11
50–59	17	4	30	14
60–69	9	0	11	4
70–79	8	0	4	6
Total	96	40	140	62
Mean age	40·4	26·2	39·7	41·8

Table 2 *Average age of subjects, and genetic group*

Age group	Dominant	X-linked	Isolated	Recessive
0–19	12·7	12·0	14·3	12·2
20–39	28·8	29·5	29·7	28·2
40+	57·1	50·2	53·2	55·1

Table 1 summarises the age spectrum and number of patients within each type of RP. Based on the Scheffé multiple comparisons procedure, with alpha =0·05, an analysis showed no differences of mean age among autosomal dominant, autosomal recessive, and isolated cases; however, the average age of X-linked recessive patients was younger than that of the other groups. Table 2 denotes the average age of subjects in three age groups for each genetic type of RP. Of our 338 RP patients 180 (53%) showed a PSC lens opacity (or were bilaterally aphakic). There was no difference between males and females in the prevalence of cataract as a function of age once the genetic group was taken into account. This was tested by determining whether the terms in a logistic regression model that involved the sex variable (that is, main effect or any interactions) were jointly significant.[8] The results indicated clearly no difference between the sexes in this context (χ^2=2·98, 6 df, p=0.81).

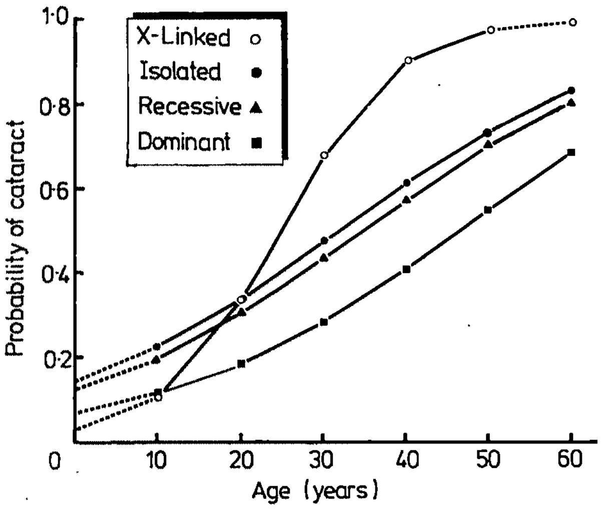

Fig. 2 *Logistic regression analysis describes the probability of posterior subcapsular (PSC) lens opacities with age for patients with different genetic types of retinitis pigmentosa. Dotted lines reflect less precision in estimating the probability of PSC changes at the upper and lower limits of the observed ages due to small sample sizes.*

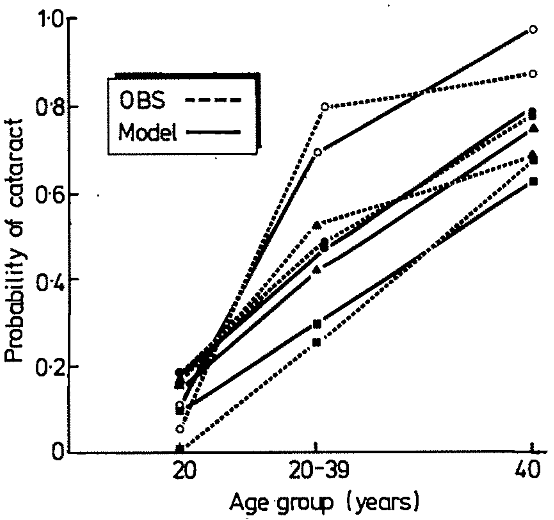

Fig. 3 *Probability of posterior subcapsular lens opacities in retinitis pigmentosa patients separated into three age groups. The solid line is determined from a logistic regression analysis model, while the dotted line is a plot of actual data (OBS). Note the close fit of the predictive model with actual data. The symbols for the different genetic types are the same as in Fig 2.*

Further analysis showed that the prevalence of cataract changed with age, as expected. However, while the rate of change of the prevalence was about the same for the autosomal dominant, autosomal recessive, and isolated groups (χ^2=2·71, 2 df, p=0·26), it was appreciably greater for the X-linked group (Fig. 2). The results depicted in Fig. 2 have been used to infer, for example, that the probability of a person with autosomal recessive disease having a cataract by age 40 years is about 57%, while the probability would be about 90% for a person with X-linked recessive disease, and about 41% for one with the autosomal dominant form of the disease. Further inspection of the regression equation indicated, as we might have expected, that the curves for autosomal recessive and isolated patients were not signficantly different (χ^2=0·24, 1 df, p=0·62). Yet additional analysis showed that not only was the X-linked recessive group distinct in terms of its greater rate of change in prevalence of lens opacities, but the autosomal dominant group was distinct in its lesser prevalence of lens opacities (χ^2=6·76, 1 df, p=0·009). We also performed an analysis of lens opacities within genetic types grouped into three age categories similar to those used in reports by other investigators.[4,5] The results with this approach were equivalent to those described in our analysis when age was used as a continuous variable (Fig. 3). Finally, we noted an expected general trend for an increase in severity of lens opacities with age within each genetic type (Cochran–Mantel–Haenszel statistic (using scored data) =63·05, 1 df, p≤0·001).[9]

Discussion

Heckenlively[5] analysed frequency and severity of PSC cataracts in 291 patients with various forms of hereditary retinal degeneration and found an overall frequency of PSC changes in 41%. His study was not directly comparable to ours, because he included patients with cone-rod degeneration, Usher's syndrome, choroideremia, and 'typical' RP. Interestingly, he reported that PSC cataracts were most common in patients with autosomal dominant RP, a finding contrary to that of our own study. The nature of this disparity is uncertain, though the difference in population samples is a possibility. Also in contrast to our findings, Heckenlively noted a significant sex preference (p=<0·002) in his group with 'sporadic' (isolated) RP in which there was a female preponderance.

Berson and coworkers[4] found a significantly greater prevalence of cataracts in X-linked recessive RP patients as compared with isolated cases in their 20–39-year age group. However, unlike our study they found no substantial differences in other age-specific group prevalences between X-linked recessive RP and isolated cases or between other genetic types such as autosomal dominant and autosomal recessive RP patients. As in our study they showed an increase in the prevalence of PSC cataracts in both eyes with age for all genetic types.

Our results stress the importance of the patient's age and genetic type in the analysis of data on the prevalence of PSC lens opacities. X-linked recessive patients appear to develop opacities more frequently and at a faster rate than patients with other genetic types of RP. As a group, patients with the autosomal dominant trait show PSC lens changes less frequently when compared with other genetic types of RP. In this regard Fig. 2 is helpful in providing specific information on the expected prevalence of PSC lens changes among the different genetic RP types with age.

This report does not resolve the pathogenetic mechanisms responsible for the development of PSC lens opacities. It does, however, point to the overall prevalence rates of lens opacities with age in a group of RP patients with different genetic types. Without consideration for genetic type our data suggest that approximately 50% of a given RP population will have PSC lens opacities or be bilaterally aphakic.

Morton F Goldberg, MD, and Maxine Gere reviewed the manuscript, and Terri Kevil and Juanita Waddy provided secretarial assistance.

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References

1 Eshaghian J, Rafferty NS, Goossens W. Ultrastructure of human cataract in retinitis pigmentosa. *Arch Ophthalmol* 1980; **98:** 2227–30.

2 Eshaghian J, Rafferty NS, Goossens W. Human cataracta complicata: clinicopathologic correlation. *Ophthalmology (Rochester)* 1981; **88:** 155–63.

3 Bastek JV, Heckenlively JR, Straatsma BR. Cataract surgery in retinitis pigmentosa. *Ophthalmology* 1982; **89:** 880–4.

4 Berson EL, Rosner B, Simonoff E. Risk factors for genetic typing and detection in retinitis pigmentosa. *Am J Ophthalmol* 1980; **89:** 763–75.

5 Heckenlively J. The frequency of posterior subcapsular cataract in the hereditary retinal degenerations. *Am J Ophthalmol* 1982; **93:** 733–8.

6 Marmor MM. The electroretinogram in retinitis pigmentosa. *Arch Ophthalmol* 1979; **97:** 1300–4.

7 Fishman GA. Retinitis pigmentosa: genetic percentages. *Arch Ophthalmol* 1978; **96:** 822–6.

8 Schlesselman JJ. *Case-control studies: design, conduct, analysis.* New York, Oxford University Press, 1982: chapter 8.

9 Landis JR, Heyman ER, Koch GG. Average partial association in three-way contingency tables: a review and discussion of alternative tests. *Int Statistical Rev* 1978: **48:** 237–54.

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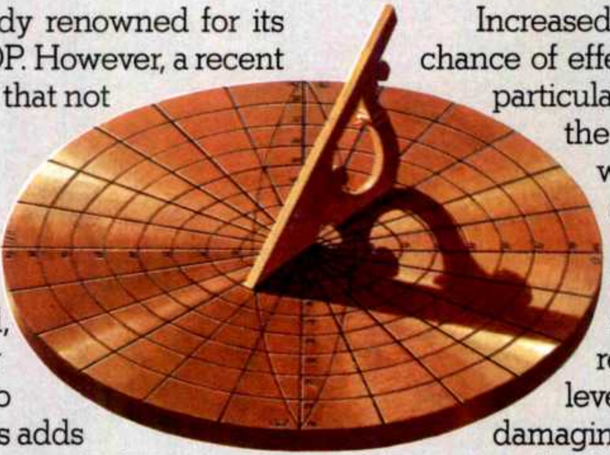

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REFERENCES
1. Sponsel, W. E., *et al.*, *Brit. J. Ophthal.*, 1983, 67, 220.
2. Norell, S. E., *Amer. J. Ophthal.*, 1981, 92, 727.
3. MacKean, J. M., and Elkington, A. R., *Brit. J. Ophthal.*, 1983, 67, 46.
4. Reynolds, P. M., *Glaucoma*, 1982, 262.
5. Willcockson, J., and Willcockson, T., *Glaucoma*, 1982, 155.

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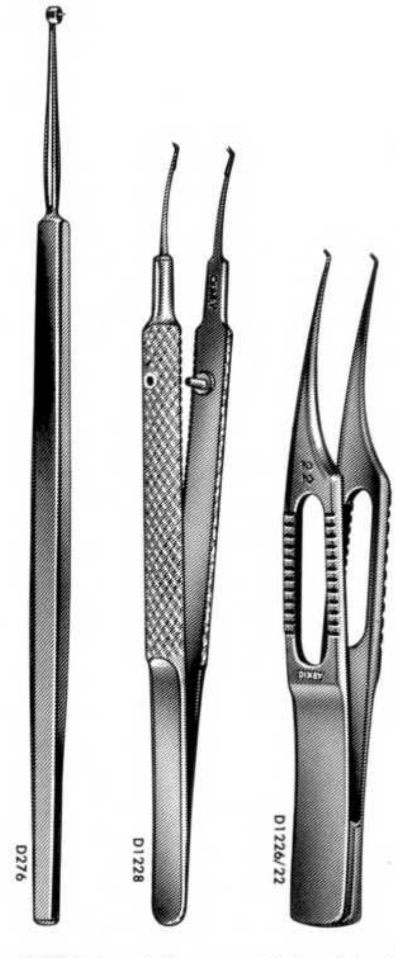

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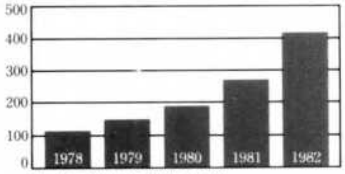

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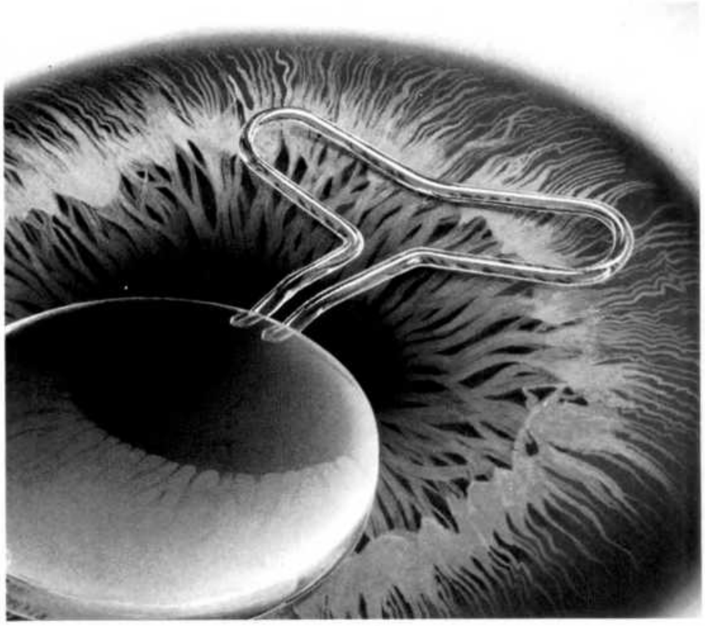

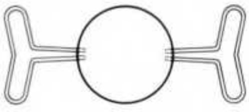

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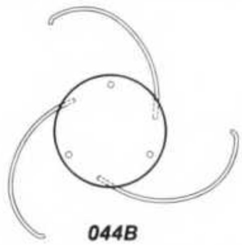

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British Journal of Ophthalmology, 1985, **69**, 267–270

Treatment of trichiasis with a lid cryoprobe

R L C JOHNSON AND J R O COLLIN

From Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY A series of 112 eyelids with symptomatic aberrant eyelashes were treated by cryotherapy using a specially designed large-surfaced high-flow nitrous oxide probe. Either thermocouple control to −20°C or timing of the application to 20 seconds (lower lid) or 25 seconds (upper lid) was used to monitor the freeze. Both techniques obtained a high cure rate and a low incidence of complications.

Misdirected and aberrant eyelashes causing symptomatic ocular discomfort are most frequently described as trichiasis, but the irritating hairs on the lid margin skin after eyelid reconstruction and the second row of lashes in congenital distichiasis also cause similar problems. Any of these types of abnormal and irritating hairs can be treated with cryotherapy to destroy their follicles.

The management of trichiasis has variously included radiotherapy,[1] surgery,[2] electrolysis,[3] and cryotherapy.[4–14] Radiotherapy and surgery, although efficacious, can result in excessive structural and functional complications and have been generally discarded except in pigmented patients where surgery can play a useful role. Electrolysis can satisfactorily destroy a hair follicle but has to be discretely, carefully, and tediously applied to each separate follicle, and although of doubtless benefit for the treatment of a few and scattered eyelashes there is a significant risk of excessive scarring of the lids if a large area or number of lashes require treatment.[3] Cryotherapy is well established as a method of eradicating hair follicles, but the standard retinal cryoprobe using either carbon dioxide or nitrous oxide as the freezing agent has an unacceptable incidence of failures (50% or greater),[5 9] and liquid nitrogen, though effective, can be technically difficult to use.[7-12] We report on our experiences with a nitrous oxide probe with a high flow rate of gas and a modified tip with a large surface area specially designed for the treatment of trichiasis of the lid margins. We believe it can provide a safe and effective instrument in all surgeons' hands.

Material and methods

The standard technique for abolishing eyelashes by the Collin cryoprobe was performed under clean but not sterile conditions. The skin was prepared for injection with an alcohol swab, and amethocaine 1% drops were instilled into the conjunctival sac. 2% Lignocaine with adrenaline (1:100 000) was locally infiltrated beneath skin and conjunctiva to obtain anaesthesia and vasoconstriction. In those patients in whom the temperature was monitored a microthermocouple was placed at the base of the hair follicles to be treated, and an insulating plate (a plastic coffee spoon) was used to protect the globe. The probe was applied from either the conjunctival or skin surface depending on the position of the targeted lashes and a thermocouple temperature reading of −20°C at the lash follicle was obtained. Later in the series the thermocouple was not used, as it had been observed that the time required to obtain the desired temperature was consistently 20 seconds in the lower lid and 25 seconds in the upper lid (Table 1). After the freeze was completed the probe was removed and the tissues allowed to thaw spontaneously until a positive temperature was recorded or until no ice formation was visible if the thermocouple was not used. No heat (e.g., irrigation) was applied to hasten the thaw. The cycle was then repeated. If multiple areas of application along the eyelid were required, an adequate freeze was ensured in the junctional areas by a slight but accurate overlap of the application sites. At the end of the freeze the offending lashes were epilated. A topical antibiotic ointment was applied and the eye firmly padded. The patients were instructed that the eyelid might be painful, usually only for a few hours during the first 12 hours,

Correspondence to J R O Collin, FRCS.

Table 1 *Relationship of recurrences to monitoring technique and causes of trichiasis*

	Patients	*Lids*	*Recurrences (time)*
A. Monitoring Technique			
Thermocouple	48	89	16 lids (14 months)
Timing	14	23	2 lids (7·4 months)
B. Diagnosis			
Idiopathic trichiasis (chronic blepharitis, glaucoma therapy, unknown)	36	54	11 lashes/6 lids (8 months)
Herpes zoster ophthalmicus	2	3	Nil
Congenital distichiasis	7	24	30 lashes/10 lids (10 months)
Fine skin hairs after lid reconstruction	4	5	Nil
Cicatrising conjunctival disease (Stevens-Johnson syndrome, mucous membrane pemphigoid, alkaline burn, radiation)	10	21	1 lash/1 lid (7 months). 2 postradiotherapy lids failed
Others (Rothmund syndrome, Romberg's hemifacial atrophy, 7th nerve palsy)	3	5	Nil
Total	62	112	18 lids

and were instructed to take minor analgesics as required. They were warned to expect some swelling and redness which would persist for 5–10 days. The pad was removed at home after 36 to 48 hours, and topical antibiotic drops and ointment were used until the swelling settled. They were seen after 10 days and again after six weeks. Any residual lashes were epilated at these times—the dead follicles releasing their lashes without discomfort or effort.

Results

Sixty-two patients, a total of 112 eyelids, were treated with the cryoprobe and included in this study. Forty-eight patients—89 eyelids—were monitored with thermocouple control, and 14 patients—23 eyelids—were monitored by timing to 25 seconds (upper lid) or 20 seconds (lower lid). The patients were seen in the clinic and the presence or absence and number of lashes was noted. A total of 23 patients (32 eyelids) were unable to attend the clinic after the minimum six-month follow-up time but replied to a questionnaire and were included in the study. They were deemed to be clear of lashes only if no ocular irritation persisted. If any symptoms were present, they were seen in the clinic before inclusion in this review. The follow-up ranged from a minimum of six months to 36 months, and the average for all eyelids was 14 months. The average for lids monitored by timing rather than thermocouple control was 7·4 months. The primary overall success rate for abolition of aberrant lashes was 84% (94:112), and in the 23 eyelids under timing control only two eyelashes (one lash in different lids in different patients) recurred, and thus this therapy provided a 91% cure rate.

The diagnostic subgroups are given in Table 1. Of the 112 lids involved in the study four had been treatment failures from previous cryotherapy using the retinal cryoprobe. Table 1 also shows in which groups the recurrences occurred. In the group monitored with timing only, the recurrence rate was 9%, which represented one recurrent eyelash on two separate eyelids. The overall recurrence rate was 16%. Six patients (with a total of 13 treated eyelids—i.e., 11% of all lids) had an average of two recurrent lashes per patient, and these were amenable to electrolysis. The only complete failure was in a patient who had previously undergone radiotherapy for a sphenoidal ridge meningioma and later had cryotherapy to the ipsilateral scarred eyelids. She underwent a second cryotherapy treatment, which completely succeeded in ablating all lashes without loss of lid tissue. There were four patients who developed aberrant eyelashes in areas that had not previously been treated. These were not considered to be either recurrences or complications. Whether they were cases of cryotherapy stimulating the adjacent eyelid to produce trichiasis type lashes, progressive disease, or an inadequate extent of initial cryoprobe application remains uncertain. Of the seven patients and 24 eyelids with congenital distichiasis who were treated with cryotherapy three patients had recurrences in a total of 10 eyelids. One patient needed electrolysis for two lashes and two brothers needed more extensive electrolysis for 2–6 abnormal lashes persisting on each eyelid. Significantly, none of the normal lashes which it was intended to preserve were destroyed by the cryotherapy.

In the entire series only four patients had lid swelling judged as marked. The worst case developed a conjunctival pseudomembrane and hemifacial oedema which spread into the neck following simultaneous treatment of two eyelids on the same side. The four patients with excessive swelling were not related to any particular diagnostic group: three of them had non-specific trichiasis and one had ocular pemphigoid. All patients had been warned of depigmentation. In this series the only non-white Caucasian patients were two Orientals and neither had significant cosmetic depigmentation. Of the 60 white Caucasian patients only one complained of depigmentation. Interestingly, one patient showed an increase in pigment in the area treated. This was best seen with the slit-lamp as tiny intraepithelial freckles. One patient with chronic blepharitis and trichiasis developed a small lid notch, but in the other cases, including those with reconstructed eyelids, there was no loss of tissue or necrosis, though some slight lid thinning could be observed if extensive areas of the eyelid had been treated.

Discussion

The biological effect of freezing has been documented by earlier investigators.[10 15] To review very briefly the features of cryobiology pertinent to the treatment of trichiasis, it has been established that a temperature of approximately −20°C is necessary to destroy hair follicles and −30°C to destroy tumour cells, but skin melanocytes are susceptible to higher temperatures of about −10°C.[10 12 15] These temperatures are the temperature present in the lesion or follicle, not on the skin or probe surface. The cryosurgical result is dependent on a rapid freeze and a slow thaw, and the actual effect is greatly improved if a double cycle freeze-thaw, freeze-thaw, is used.[10 15] Local vasoconstriction, by means of a local anaesthetic that contains adrenaline, improves the efficiency of the treatment by increasing the depth of the freeze and prolonging the thaw stage.

The treatment of trichiasis with freezing has been successfully performed with liquid nitrogen or nitrous oxide probes, and the thermocouple has been essential.[7 12 13] Liquid nitrogen, with the very low boiling point of −195°C is a very effective cryo agent, but has the disadvantages of the liquid spreading and running during its application, difficulty of storage, and logistics of acquisition and maintenance.[12 13] It is, however, effective.[7] Nitrous oxide, although not as efficient a heat sink as liquid nitrogen, has a lower boiling point than carbon dioxide (−90°C versus −30°C) and thus is more effective than that gas.[15] Nitrous oxide probes, in the form of cryoprobes, have been limited by low flow systems and small surface areas which limit the efficiency of obtaining an adequate freeze. In the treatment of trichiasis a 50% or higher failure rate has been reported with them.[5 9] To utilise the convenience of the nitrous oxide probe and to improve on the inadequate freezing potential of retinal cryoprobes, a high flow and large surfaced (10×4×3 mm) probe with two differently orientated surfaces for ease of application has been especially designed for use on eyelids. With thermocouple monitoring to −20°C 89 eyelids were treated, with a high success rate. The duration of the application necessary was observed to be consistently 20 seconds for the lower lid and 25 seconds for the upper lid. In the last 23 eyelids the cryosurgical application was monitored by timing for these periods without using a thermocouple. Satisfactory results after a minimum six-month follow-up were obtained.

The overall success rate for the abolition of aberrant lashes was 84% of eyelids (94/112) in 84% of patients (52/62). Since only one lash recurred in six lids and four lashes recurred in two lids, all but 10 eyelids were amenable to minor electrolysis to achieve a cure rate of 91%. Of the remaining 10 eyelids, the two postradiotherapy eyelids were cleared of eyelashes with a second cryotherapy treatment, and the other recurrences were mainly in the distichiasis group and required more extensive electrolysis. The diagnostic group with the highest failure rate was these congenital distichiasis patients, of whom three out of seven (nine out of 23 eyelids) had recurrences. However, since these occurred where the stated goal was to spare normal eyelashes, it is likely that the cryotherapy was not applied adequately. The other diagnostic groups, including subgroups for lid reconstruction and cicatrising conjunctival disease, had no particular failure or complication tendency. Our overall success rate of 84% is about the same as that reported by Wood and Anderson (90%)[13] and Sullivan (88%)[11] using nitrous oxide. It was much higher than when a retinal probe was used.[5 9] If the patients with congenital distichiasis are omitted, our results are similar to those reported by Fraunfelder and Petursson using liquid nitrogen (90%+).[7]

Wood and Anderson[13] report an incidence of complications of 18% when using a nitrous oxide probe on the eyelids in the treatment of trichiasis. We suffered a 10% eyelid complication rate. Four patients suffered marked postoperative oedema, and one of these had a pseudomembrane. These patients had been suffering from idiopathic trichiasis (three patients) or ocular pemphigoid (one patient). All the complications in our patients resolved except for one patient with trichiasis who was left with a lid notch. One patient had cosmetically evident depigmentation, and one had microscopic evidence of hyperpigmentation which was insignificant to the unaided eye. Unlike Wood and Anderson's series[13] the diagnostic subgroups of cicatrising conjunctival disease and reconstructed lids did not have excessive complications. No corneal disease, acceleration of cicatrisation, or activation of herpes zoster occurred. Thus we have not found cryotherapy to be contraindicated in these patients.

We conclude that by using the probe and technique described it is possible consistently to obtain a very high rate of eradication of hair follicles with a low risk of complications and without necessarily using a thermocouple.

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References

1 McDonald JE, Wilson FM. Ocular therapy with beta particles. *Trans Am Acad Ophthalmol Otolaryngol* 1959; **63:** 468–85.

2 Clorfeine GS, Kielor RA. Lash excision in trichiasis. *Ann Ophthalmol* 1977; **9:** 525–8.

3 Soll DB. *Management of complications in ophthalmic plastic surgery*. Birmingham, Alabama: Aesculapius, 1976.

4 Sullivan JH, Beard C, Bullock JD. Cryosurgery for treatment of trichiasis. *Am J Ophthalmol* 1977; **82:** 117–21.

5 Collin JRO, Coster DJ, Sullivan JH. Cryosurgery for trichiasis. *Trans Ophthalmol Soc UK* 1978; **98:** 81–3.

6 Fraunfelder FT, Farris HE, Wallace TR, *et al*. The role of cryosurgery in external ocular and periocular disease. *Trans Am Acad Ophthalmol Otolaryngol* 1977; **83:** 713–24.

7 Fraunfelder FT, Petursson GJ. The use of liquid nitrogen cryospray for treatment of trichiasis. *Ophthalmic Surg* 1979; **10:** 42–6.

8 Hecht SD. Cryotherapy of trichiasis with use of the retinal cryoprobe. *Ann Ophthalmol* 1977; **90:** 1501–3.

9 Majekodunmi S. Cryosurgery in treatment of trichiasis. *Br J Ophthalmol* 1982; **66:** 337–9.

10 Soll DB, Harrison SE. Basic concepts and an overview of cryosurgery in ophthalmic plastic surgery. *Ophthalmic Surg* 1979; **10:** 31–6.

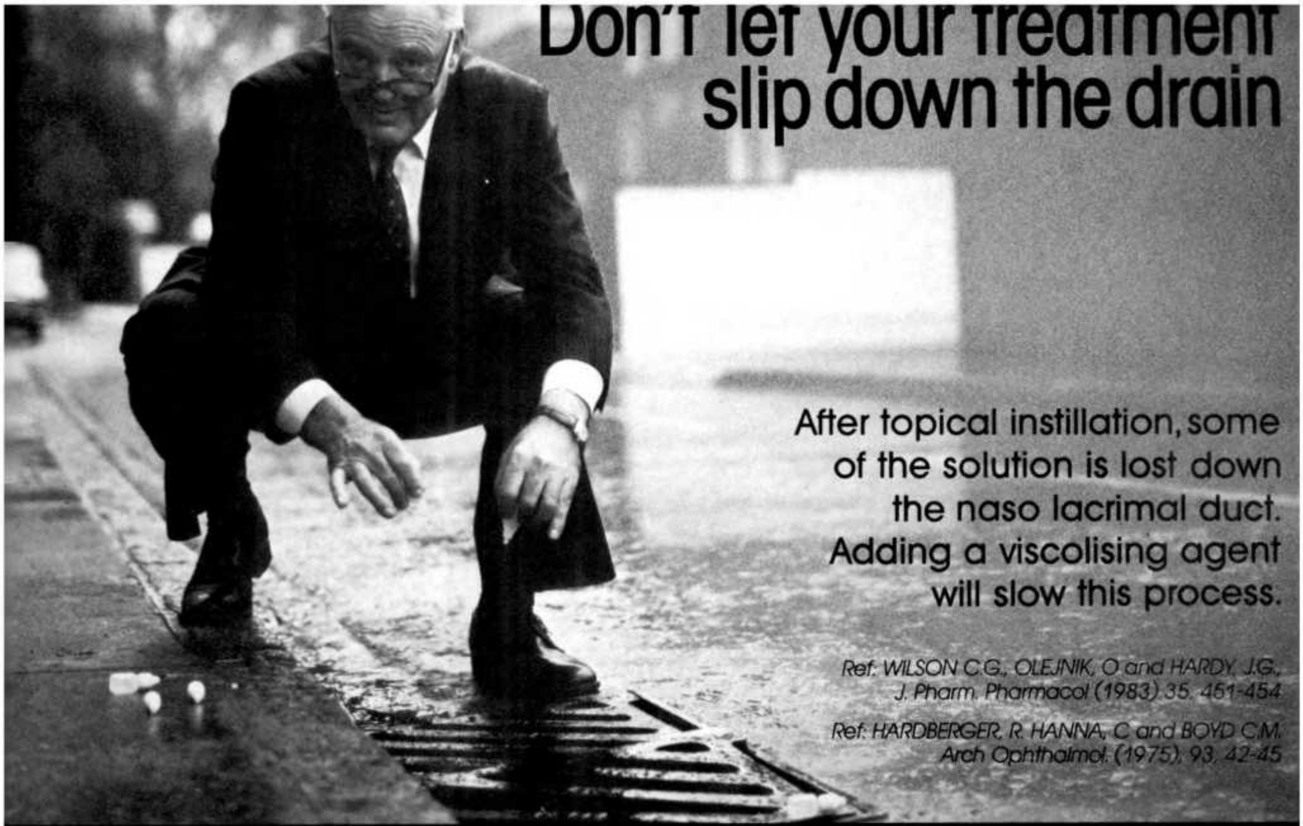
11 Sullivan JH. The use of cryotherapy for trichiasis. *Trans Am Acad Ophthalmol Otolaryngol* 1977; **83:** 708–12.

12 Sullivan JH. Cryosurgery in ophthalmic practice. *Ophthalmic Surg* 1979; **10:** 37–41.

13 Wood JR, Anderson RL. Complications of cryosurgery. *Arch Ophthalmol* 1981; **99:** 460–3.

14 Wingfield DL, Fraunfelder FT. Possible complications secondary to cryotherapy. *Ophthalmic Surg* 1979; **10:** 47–55.

15 Wilkes TDI, Fraunfelder FT. Principles of cryosurgery. *Ophthalmic Surg* 1979; **10:** 21–30.



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References: 1. Cagle, G.D. and Abshire, R.L.: "Quantitative Ocular Bacteriology: A Method for the Enumeration and Identification of Bacteria from the Skin Lash Margin and Conjunctiva." Investigative Ophthalmology and Visual Science 20:751-758 (June) 1981. **2.** Data on file, Alcon Laboratories, Inc. **3.** Smith, J.P.: Data on File, Alcon Laboratories, Inc. **4.** Cagle, G. et al.: "Topical Tobramycin and Gentamicin Sulfate in the Treatment of Ocular Infections: Multicenter Study." Current Eye Research 1:523-534, 1982.

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Large bimedial rectus recessions in congenital esotropia

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SUMMARY The success rate of large (6 and 7 mm) bimedial rectus recessions in 45 congenital esotropes with deviations of 50 prism dioptres or greater was found to be 91%. Judgment of final alignment was made six weeks postoperatively, with an average follow-up of 13 months. Large bimedial rectus recessions are an effective surgical treatment for congenital esotropia. This procedure does not significantly alter adduction, and leaves other muscles available should further surgery be necessary. These findings show that initial surgery on three or more muscles is unnecessary in congenital esotropia.

The management of congenital esotropia has long been a topic of controversy, not only concerning when to operate but also as to the best surgical approach. Success rates ranging from 40 to 80% have been described with a variety of surgical techniques.[1-8] This paper shows that bimedial rectus recessions in excess of the traditional 5 mm have a high success rate in the management of the congenital esotrope with a deviation of 50 prism dioptres or greater.

Materials and methods

The records of 218 patients with congenital esotropia who underwent surgery at the Wills Eye Hospital between 1979 and 1983 were reviewed. Forty-five patients met the criteria for inclusion in this study, which were as follows: (1) esotropia documented by one of the authors before 6 months of age, (2) preoperative deviation of 50 prism dioptres or greater, (3) alternation of fixation, (4) correction of hyperopic refractive errors greater than 2 dioptres with spectacles, (5) age at operation less than 2 years, (6) no overt evidence of central nervous system abnormalities or organic eye disease, and (7) follow-up of six weeks or more. Deviations were evaluated by the Hirschberg or Krimsky methods, or by the prism and cover test at distance when possible. Cycloplegic refraction with 1% cyclopentolate and in some cases 1% atropine was performed in all cases.

All patients underwent bimedial rectus recessions of 6 or 7 mm by the Parks cul-de-sac approach. For this study an alignment within 10 prism dioptres of orthophoria at six weeks postoperatively was considered a success.

Results

Thirty-seven patients had deviations in the 50 to 65 prism dioptre range and underwent bimedial rectus recessions of 6 mm. The remaining eight patients had deviations in excess of 70 prism dioptres and had bimedial rectus recessions of 7 mm. The average deviation in the 6 mm group was 59·7 prism dioptres of esotropia, and the average for the 7 mm group was 76·9 prism dioptres. Refractive errors ranged from −1·50 to +4·50 dioptres (average +1·26 dioptres) for the 6 mm group, and plano to +2·50 dioptres (average +1·38 dioptres) for the 7 mm group (Tables 1–3).

Of the 37 patients who underwent 6 mm recessions 33 (89%) were considered successful at six weeks, whereas all eight patients (100%) in the 7 mm group were successful. Overall 91% of both groups combined were successful. In addition no clinically significant limitation of convergence or adduction was noted in any of the patients.

For this report the final surgical result was judged at six weeks, with follow-up ranging from two months to four and a half years and averaging 13 months. Two children (4·4%), one in the 6 mm and one in the 7 mm group, required second operations for esotropia at 10 and 28 months after the first surgery

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Table 1 *Results of 6 mm bimedial rectus recessions*

Patient	*Age at surgery (mos).*	*Preop. deviation (Δ)*	*Refractive error (D)*	*6-Wk. postop. alignment*	*Follow-up (mos).*	*Comments*
1	8	65	+2·50	S*	42	Developed accommodative ET
2	9	60	+1·75	S	7	
3	18	55	+1·50	S	3	
4	19	55	+2·50	S	10	
5	24	55	plano	S	24	
6	7	60	plano	S	10	
7	12	55	+1·50	S	24	
8	7	55	+3·00	S	12	
9	5	65	+2·00	S	3	
10	9	55	+2·25	S	6	
11	17	65	+1·50	S	48	Redeveloped ET 10 mos. postop.→Reoperation
12	18	55	−1·50	S	6	
13	14	65	+0·75	S	8	
14	7	65	+0·50	S	12	Developed accommodative ET
15	24	65	+1·00	S	9	
16	7	55	+1·75	S	12	
17	16	60	+0·50	S	10	
18	12	55	+4·50	S	2	
19	6	55	+1·50	S	4	
20	15	65	+1·00	S	6	
21	22	55	+1·50	S	12	Developed accommodative ET
22	5	60	−0·25	S	17	
23	24	65	+1·50	S	2	
24	23	55	plano	S	36	
25	9	55	+0·50	S	3	
26	18	60	+0·25	S	6	
27	8	55	+2·75	S	12	
28	20	75	+2·50	S	7	Developed accommodative ET
29	11	65	+0·50	S	26	
30	5	55	+3·00	ET=30	18	LR resections 8 mos. later MR rerecessed 20 mos. later
31	11	65	−1·25	ET=20	12	LR resections 12 mos. later
32	8	55	+2·50	S	3	
33	5	65	plano	ET=35	12	MR rerecessed 4 mos. later
34	7	65	+1·50	ET=25	12	LR resections 3 mos. later
35	11	65	plano	S	3	
36	16	55	+1·25	S	3	
37	6	55	+2·00	S	2	

*Successful alignment (ET≤10Δ).

respectively. Five children (11%) redeveloped esotropia that was corrected with hyperopic spectacles. The esotropia redeveloped from three to 36 months after surgery, with an average of 13 months. Refractive errors ranged from +0·50 to +2·50 dioptres in this group, with an average of 1·9 dioptres of hyperopia. None of the patients in this study developed a consecutive exotropia.

Discussion

A variety of surgical techniques for the correction of congenital esotropia have been described. Two basic 'schools' have emerged as to the type of surgical procedure, those advocating uniform surgery and those who prefer a selective approach. Proponents of uniform surgery advocate step-wise surgery, the first operation being symmetrical bimedial rectus recessions or a medial rectus recession combined with a lateral rectus resection on the non-fixating eye. Further surgery, either bilateral rectus resections or a medial rectus recession and lateral rectus resection on the fellow eye, is performed as necessary. A successful operation is generally accepted as one which results with an alignment within 10 prism dioptres of orthophoria.[1-5 7 9] The success rate for the uniform approach after one operation was 50% in the series of Ing and co-workers[1] and 42% in von Noorden's series.[2] Helveston and colleagues[3] initially reported a 72% success rate by his augmented recession technique, consisting of a graded bimedial rectus recession (maximum recession of 5·5 mm) with the measurement carried out from the limbus. This was combined with recession of the conjunctiva and Tenon's capsule. More recently they described an approximately 80% success rate using this technique.[4]

Table 2 *Results of 7 mm bimedial rectus recessions*

Patient	*Age at surgery (mos).*	*Preop. deviation (Δ)*	*Refractive error (D)*	*6-Wk. postop. alignment*	*Follow-up (mos).*	*Comments*
1	6	75	+2·00	S*	2	
2	8	80	+1·50	S	3	
3	7	75	+0·50	S	54	
4	9	75	+2·50	S	30	Developed accommodative ET
5	8	75	plano	S	48	Developed ET 28 mos. postop.→Reoperation
6	8	75	+2·50	S	7	
7	6	75	+1·00	S	3	
8	6	85	+1·00	S	4	

*Successful alignment (ET≤10Δ).

Table 3 *Summary of clinical data*

	Bimedial rectus recessions	
	6 mm group	*7 mm group*
Average deviation	59·7Δ	76·9Δ
Average refraction	+1·26D	+1·38D
Success rate	33/37 (89%)	8/8 (100%)
Average follow-up	12 mos.	19 mos.
Reoperation rate	1/37 (2·7%)	1/8 (12·5%)

A selective approach has also been suggested, with surgery on two to four of the horizontal rectus muscles, depending on the size of the deviation. Foster and co-workers[5] described a 79% success rate with one operation using this approach. Lee and Dyer[6] recently recommended that bimedial rectus recessions and bilateral rectus resections be performed in congenital esotropes with a deviation in excess of 50 dioptres. The eyes of 61% of their patients were straight after one operation.

Other authors have suggested bimedial rectus recessions in excess of the traditional 5 mm in patients with large angle esotropia. Hess and Calhoun[9] reported on 30 patients ranging in age from 5 months to 12 years (with an average age of 4 years) with large angle esotropia who underwent graded bimedial rectus recessions of 6 to 8 mm. 84% of the patients in the 6 mm group and 60% in the 7 mm group were within 10 prism dioptres of orthophoria with the initial procedure, whereas the one patient who had 8 mm recessions was undercorrected.

The results of the present study corroborate the experience of Prieto-Diaz,[7] who was an early advocate of large bimedial rectus recessions for congenital esotropia. Slightly over 80% of his 85 patients had successful realignment which remained stable over a three-year follow-up period. These results are similar to those of Rodriguez-Vazquez,[8] who also reported a success rate of approximately 80%. In spite of the large recessions performed, both adduction and convergence were not affected significantly in either of these studies.

We considered the alignment at six weeks postoperatively to represent the final surgical result in this study. Helveston *et al.*[3] used the six-week postoperative alignment as the final surgical result for statistical purposes in analysing his augmented recession technique. Parks[10] reoperates on patients who have residual esotropia angles of 15 prism dioptres or more at six weeks postoperatively.

Recently Bateman and co-workers[11] utilised computer based discriminant analysis to study the results of congenital esotropia surgery. They discovered that the preoperative deviation, amount of medial rectus recession, and the interval between the onset of the esotropia and surgery were all statistically significant predictive variables for the surgical outcome six weeks postoperatively. In addition they found that only the postoperative deviation at six weeks was predictive of the long-term deviation, with a minimum follow-up of six months in their series.

Freeley and co-workers[12] recently reported on a group of patients with congenital esotropia who were surgically aligned prior to 18 months of age. They found that 28% of these patients later redeveloped esotropia, with an average time of onset at 14 months postoperatively. 78% of this group were corrected with hyperopic spectacles. Five patients (11%) in the current study fell into this category, and the eyes of all were straightened with glasses. Therefore a significant number of patients with congenital esotropia who are surgically corrected may redevelop a convergent deviation which can be successfully treated with even a mild hyperopic correction.

The bimedial recession approach is preferred by those who favour symmetrical surgery. Recessions are technically easier than resections, thus requiring less anaesthesia time.[9] Because the tendon rather than muscle is severed in recessions, there is less tendency toward bleeding. Bimedial rectus recessions also leave the lateral rectus muscles untouched should further surgery be necessary.

Contrary to the selective approach for large angle congenital esotropia and from a study of our findings, we consider that initial surgery on three or more muscles is not indicated.

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References

1 Ing M, Costenbader FD, Parks MM, Albert DG. Early surgery for congenital esotropia. *Am J Ophthalmol* 1966; **61:** 1419–27.

2 Noorden GK von, Isaza A, Parks ME. Surgical treatment of congenital esotropia. *Trans Am Acad Ophthalmol Otolaryngol* 1972; **76:** 1465–78.

3 Helveston EM, Ellis FD, Patterson JH, Weber J. Augmented recession of the medial recti. *Ophthalmology* 1978; **85:** 507–11.

4 Helveston EM, Ellis FD, Schott J, *et al.* Surgical treatment of congenital esotropia. *Am J Ophthalmol* 1983; **96:** 218–28.

5 Foster RS, Paul TO, Jampolsky A. Management of infantile esotropia. *Am J Ophthalmol* 1976; **89:** 291–9.

6 Lee DA, Dyer JA. Bilateral medial rectus muscle recession and lateral rectus muscle resection in the treatment of congenital esotropia. *Am J Ophthalmol* 1983; **95:** 528–35.

7 Prieto-Diaz J. Large bilateral medial rectus recession in early esotropia with bilateral limitation of abduction. *J Pediatr Ophthalmol* 1980; **17:** 101–5.

8 Rodriguez-Vazquez R. Retroinsercion amplia en cirugia de endotropias alternas. Actas del IV Congreso del Consejo Latino Americano de Estrabismo, Mexico 1974: 169.

9 Hess JB, Calhoun JH. A new rationale for the management of large angle esotropia. *J Pediatr Ophthalmol* 1979; **16:** 345–8.

10 Parks MM. Concomitant esodeviations. In: Duane TD, Jaeger EA, eds. *Clinical ophthalmology*. Hagerstown: Harper and Ros, 1982: **1:** 10.

11 Bateman JB, Parks MM, Wheeler N. Discriminant analysis of congenital esotropia surgery. *Ophthalmology* 1983; **96:** 1146–53.

12 Freeley DA, Nelson LB, Calhoun JH. Recurrent esotropia following early successful surgical correction of congenital esotropia. *J Pediatr Ophthalmol* 1983; **20:** 68–71.

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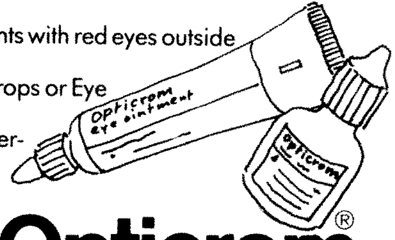

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References: 1. Riddington, C., 'A survey of non-seasonal conjunctivitis' 1982 (data on file).
2. Hennawi, M., British Journal of Opthalmology, 1980, 64, 483-486.

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Prostaglandin levels in human vitreous

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SUMMARY Vitreous samples were obtained from 41 eyes undergoing vitrectomy, and radioimmunoassays were performed to measure concentrations of the prostaglandins PGE_2, $PGF_{2\alpha}$, prostacyclin, and thromboxane. Presumably physiological levels (approximately 100 picograms/ml) were found in vitreous from eyes undergoing cataract extraction. Eyes with vitreous haemorrhage, retinal detachment, or cystoid macular oedema had similarly low levels. Vitreous prostaglandins were mildly elevated in trauma and endophthalmitis and markedly elevated in aphakic bullous keratopathy. The role prostaglandins may play in cystoid macular oedema is reviewed.

Prostaglandins are important mediators of inflammation, and the synthesis of these vasoactive prostaglandin compounds (PGE_2, $PGF_2\alpha$, prostacyclin [PGI_2]) by ocular tissues has been demonstrated. Low levels of these prostaglandins are found in normal human aqueous. A variety of conditions in which anterior chamber inflammation is present (keratitis, paracentesis, panretinal photocoagulation, etc.) have higher aqueous levels.[1-4] Elevated aqueous levels have also been found in association with aphakic cystoid macular oedema. Several investigators believe that prostaglandins synthesised in the anterior segment (as in iris and ciliary body) diffuse through the vitreous and then act on retinal capillaries to produce macular oedema.[5 6] Miyake, Yannuzzi, Klein, and others have reported clinical trials in which a topical or oral prostaglandin inhibitor, indomethacin, given preoperatively and in the early postoperative period was associated with a lower incidence of fluorescein angiographic aphakic cystoid macular oedema.[7-11] Miyake also noted concurrent reduction in aqueous prostaglandin levels and clinical improvement in the cystoid macular oedema. Furthermore, Miyake *et al.* have reported [12] elevated aqueous prostaglandins in eyes which developed cystoid macular oedema after intracapsular cataract extraction with vitreous loss and vitreous incarceration to the wound. Pars plana vitrectomy led to lower aqueous prostaglandins and improvement in the oedema of relatively short duration.[12]

Despite extensive speculation that prostaglandins, which are synthesised anteriorly, pass through the vitreous and play a pathological role in the posterior pole, concentrations of prostaglandins in the vitreous itself have not been reported either in normal or in diseased eyes. We have therefore measured vitreous prostaglandin levels in 41 eyes, two of which had cystoid macular oedema, and have identified factors possibly associated with elevated vitreous prostaglandins.

Materials and methods

Vitreous specimens were obtained during intraocular surgery on 41 eyes. In six cases vitreous presentation occurred during cataract extraction, thus necessitating an anterior vitrectomy. Fifteen eyes had vitreous haemorrhage. Six had retinal detachment without vitreous haemorrhage, five had aphakic bullous keratopathy (ABK), for which penetrating keratoplasties and anterior vitrectomies were performed; three had trauma, two had cystoid macular oedema, one had endophthalmitis, and three had miscellaneous indications for vitrectomy. To allow accurate determination of prostaglandin concentration we attempted to remove specimens from the eye before dilution by balanced salt solution (BSS) infusion occurred. In the 18 anterior vitrectomies (44% of the total), this was accomplished by an 'open sky' tech-

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nique. With the cornea retracted, the VISC-10 vitrectomy instrument tip was placed directly in formed vitreous and the specimen was cut, aspirated, and removed from the system before any infusion was begun. In the 24 pars plana vitrectomies (56% of the total) the VISC-10 tip was directly visualised through the pupillary space in formed vitreous. An initial sample (usually about 1cm^3) was cut, aspirated, and removed from the system prior to starting BSS infusion. In each case the vitrectomy instrument was in view at all times and was cutting without exerting traction on the vitreous base. As vitreous volume decreased, slight scleral infolding was occasionally observed, but no intraoperative damage to the retina or lens was seen in any of the cases. Infusion was begun immediately if there was any question of tractional forces on the retina. In only seven of the 41 cases was infusion necessary before the specimen was obtained. In these cases the surgeon estimated the percentage dilution at the time of the procedure.

To minimise artefactual prostaglandin synthesis the vitreous was immediately transferred into tubes containing 0·5 ml (10 μg) of indomethacin. The tubes were kept on ice, centrifuged for 10 minutes at 4000 rpm to remove cellular debris, and then stored at −70°C until assays could be performed. Prostaglandins (PG) were measured by the double antibody radioimmunoassay technique of Levine[13] with modifications.[14] Briefly, antisera were raised against each PG by immunising rabbits with PGE_2, $PGF_2\alpha$, 6-keto-$PGF_1\alpha$ (the chemically stable transformation product of PGI_2) and TXB_2 (the chemically stable product of thromboxane A_2) coupled to human serum albumin. 0·1 ml of vitreous fluid was added to 100 μl rabbit anti-PG antibody (in 0·1 M Tris buffer, pH 7·4) and 100 μl tritiated PG. The mixture was incubated at 37°C for one hour. 0·1 ml of normal rabbit serum (1:25 dilution) and 100 μl goat anti-rabbit globulin (1:8 dilution) were then added. After thoroughly mixing the reaction mixture was incubated at 4°C overnight. The antibody-bound tritiated PG was sedimented by centrifugation, the supernatant was discarded, and the precipitate was counted for radioactivity.

There was less than 1% cross-reactivity between the PGE_2 antibody and $PGF_{2\alpha}$, 6-keto-$PGF_{1\alpha}$, and TXB_2; between the $PGF_{2\alpha}$ antibody and PGE_2, 6-keto-$PGF_{1\alpha}$, and TXB_2; or between the TXB_2 antibody and PGE_2, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$. The lowest limit of sensitivity of these assays was 10 pg/ml, and the intra-assay coefficient of variation was less than 10%.

To evaluate further the validity and accuracy of these radioimmunoassay techniques, 6-keto-$PGF_1\alpha$ was added to eight samples. Analysis of these specimens by radioimmunoassay showed a recovery of 101±7%.[15] Similarly, assays performed before and after the addition of PGE_2 showed a recovery of 75±19%. In addition plasma levels of prostaglandins measured by the radioimmunoassay procedures described above are similar to those determined by gas chromatography/mass spectrophotometry.[16]

Results

A brief clinical description of the cases and prostaglandin concentrations are listed in Table 1. Table 2 gives the mean prostaglandin levels for each group of cases. Ages ranged from 28 to 88 years with 70% between 60 and 79. Thirty-seven were men, four were women. Thirty-five of the 41 were Caucasian. Preoperatively visual acuity was less than 20/200 in 30 of the eyes (73%). Twenty-seven (66%) were phakic, 14 (34%) aphakic. Fifteen eyes (37%) had conjunctival injection and/or anterior chamber reaction as evidence of anterior segment inflammation (graded 0 to 4+ in Table 1.) Follow-up was greater than six months in 20 eyes, three to six months for 12 eyes, and for nine eyes the patient was either lost to follow-up or died within three months. Visual acuity improved or remained the same in 31 eyes, decreased in five eyes and five eyes were lost to follow-up. Postoperatively three eyes had slight progression of pre-existing cataracts (nuclear sclerosis); no new cataracts developed. Three eyes developed recurrent retinal detachments; no postoperative detachments occurred in previously attached retinas.

It is not surprising that quiet eyes undergoing routine cataract extraction had very low, presumably physiological, concentrations of vitreous prostaglandins. The levels found in these vitreous samples corresponded well with previously reported normal aqueous levels (around 100 pg/ml).

Neither vitreous haemorrhage nor the presence of a retinal detachment produced prostaglandins in any greater concentration than in the cataract patients. Since there was no appreciable inflammation in these eyes, the low levels are what would be expected.

In three of the five ABK eyes PGE_2 levels were greater than 1000 pg/ml with a mean value of 2569 pg/ml. It is unknown whether prostaglandins may play a causative role in such cases of corneal decompensation or whether elevated levels are coincidental. It is known that principal sites of PGE_2 synthesis are the iris and ciliary body. In the case with the highest level (10 000 pg/ml) dense vitreous adhesions to the iris and Copeland intraocular lens were present. Traction by vitreous strands on the iris/ciliary body may thus have stimulated prostaglandin synthesis.

One of the miscellaneous cases with synechiae

Table 1 *Vitreous prostaglandin levels*

Case	*Age*	*Sex*	*Diagnosis**	*Vision*	*Phakic*	*Inflam.*	*Procedure†*	*Final‡ VA*	*PGE_2*	*$PGF_{2\alpha}$*	*6-keto-$PG_{2\alpha}$*	*TX*
Cataracts												
1§	58	M	Cataract	20/200	Yes	0	ICCE, ant. vit.	20/30	0	0	0	0
2	84	M	Cataract	20/200	Yes	0	ICCE, ant. vit.	20/60	0	275	92	0
3	48	M	Cataract	20/80	Yes	0	ECCE, ant. vit.	20/30	332	262	—	—
4	58	M	Cataract, subluxed	20/400	Yes	0	ICCE, ant. vit.	20/30	0	0	0	—
5	59	M	Cataract, subluxed	20/400	Yes	0	ICCE, ant. vit.	LP	142	109	0	—
6	68	M	Cataract	20/200	Yes	0	ECCE, ant. vit.	20/25	373	778	156	—
Vit. Haem.												
7	58	M	Vit. haem., RD, PDR	HM	Yes	0	PPV	20/200	0	285	61	0
8	52	M	Vit. haem., RD, PDR	HM	Yes	0	PPV	HM	0	450	0	42
9	53	M	Vit. haem., RD, PDR	1/200	Yes	0	PPV	LP	0	0	102	—
10§	56	M	Vit. haem., RD, PDR	CF 2 feet	Yes	0	PPV	CF 3 feet	0	0	—	—
11§	49	M	Vit. haem., RD, PDR	HM 1 foot	Yes	0	PPV	Died	0	0	0	0
12	52	M	Vit. haem., RD, PDR	HM	Yes	0	PPV	NLP	0	0	—	—
13	57	M	Vit. haem., PDR	CF	No	0	PPV	LP	0	45	0	—
14	67	M	Vit. haem., RD, PDR	HM	Yes	0	PPV	10/100	75	18	15	—
15	54	M	Vit. haem., RD, PDR	HM	Yes	0	PPV	LP	180	234	0	—
16	65	M	Vit. haem., RD, PDR	LP	Yes	2+	Ant. vit.	LTF	135	120	0	—
17	62	M	Vit. haem., cat., PDR	HM	Yes	0	Ant. vit.	CF 4 feet	480	88	0	—
18‖		M	Vit. haem., RD, PDR	LP	Yes	3+	PPV, ICCE	20/200	281	31	225	—
19		M	Vit. haem., RD, PDR	LP	No	3+	Air-fluid exch.	20/200	0	0	0	—
20	57	M	Vit. haem., PDR	CF	Yes	0	PPV	CF 1 foot exp.	67	1800	0	—
21	65	M	Vit. haem., SMCD	CF	Yes	0	PPV	Died	406	60	650	—
RD												
22§	57	M	RD	5/200	Yes	0	PPV	20/200	0	0	0	102
23	67	M	RD	CF	No	0	PPV, SBP	20/60	0	53	0	—
24	31	M	RD	LP	Yes	2+	PPV, ICCE, SBP	LP	0	0	—	—
25	56	M	RD	HM	No	2+	PPV	20/400	0	0	0	—
26§	31	M	RD	LP	No	2+	PPV, SBP	LP	0	0	0	—
27	50	F	RD, vit. in AC	20/50	No	1+	PPV, SBP	20/15	105	720	0	—
ABK												
28§	62	M	ABK	20/200	No	1+	PPV	Died	139	0	—	—
29	79	F	ABK	1/200	No	3+	Ant. vit., PK	6/200	10 000	110	1000	—
30	78	M	ABK	2/200	No	1+	Ant. vit., PK	HM 5 feet	1050	520	640	—
31	88	M	ABK	CF	No	0	Ant. vit., PK	CF 2 feet	154	650	49	—
32	67	M	ABK	CF	No	0	Ant. vit., PK	20/200	1500	250	320	—
Trauma												
33	28	M	Intraocular FB	20/60	Yes	3+	PPV, IOFB rem.	20/25	238	—	—	—
34	52	M	Dislocated lens	HM	Yes	4+	Ant. vit. ICCE	20/30	0	0	—	—
35	60	M	Dislocated lens	CF	Yes	0	Ant. vit., ICCE	20/60	1100	1320	2600	—
CMO												
36§	59	F	CMO	20/200	No	0	PPV	20/30	0	0	0	0
37	82	F	CMO, ABK	20/200	No	2+	Ant. vit., PK	20/40	0	0	720	—
Endophthalmitis												
38	30?	M	Fungal endophthal.	20/400	Yes	0	PPV	Died	678	550	0	—
Other												
39	85	M	Cataract, glaucoma	LP	Yes	1+	Ant. vit., ICCE, trabeculectomy	20/200	0	1040	80	—
40	47	M	Loose IOL	20/50	No	2+	Ant. vit., IOL removed	20/25	46	0	0	—
41	85	M	Cat. stuck to vit.	20/80	Yes	0	Ant. vit., ICCE	20/25	34 615	332	1523	—

*Diagnoses: Cataract (cat.), vitreous haemorrhage (vit. haem.), retinal detachment (RD), proliferative diabetic retinopathy (PDR), senile macular choroidal degeneration (SMCD), anterior chamber (AC), aphakic bullous keratopathy (ABK), foreign body (FB), cystoid macular oedema (CMO), intraocular lens (IOL).

†Procedure: Intracapsular cataract extraction (ICCE), anterior vitrectomy (ant. vit.), extracapsular cataract extraction (ECCE), pars plana vitrectomy (PPV), scleral buckling procedure (SBP), penetrating keratoplasty (PK), intraocular foreign body removal (IOFB rem.), intraocular lens (IOL).

‡Final visual acuity: length of follow-up: ≥6 months: cases 1, 2, 3, 4, 5, 7, 9, 10, 12, 13, 14, 15, 17, 22, 23, 25, 33, 34, 37, 39. ≥3 months: cases 6, 8, 18, 19, 27, 30, 31, 32, 35, 36, 40, 41. <3 months or lost to follow-up (LTF): cases 11, 16, 20, 21, 24, 26, 28, 29, 38.

§Specimens diluted at time of collection. Percentage dilution estimated by surgeon.

‖Samples 18 and 19 from same patient.

Visual acuity: CF = counting fingers. HM = hand movements. LP = light perception. LTF = lost to follow-up.

Metric conversion: 1 foot = 30cm.

Table 2 *Mean vitreous prostaglandin levels*

Diagnosis	*PGE_2*	*$PGF_{2\alpha}$*	*6-keto-$PG_{2\alpha}$*	*TX*
Cataracts	141	237	49	0
Vitreous haemorrhage	108	209	81	21
Retinal detachment	17	129	0	102
Aphakic bullous ker.	2568	306	502	—
Trauma	446	660	2600	—
Cystoid macular oedema	0	0	360	0
Endophthalmitis	678	550	0	—
Other	11 553	457	534	0

between the posterior lens capsule and the anterior hyaloid face also had extremely high prostaglandin (PGE_2 34 615 pg/ml, 6-keto-$PG_{1\alpha}$ 1523 pg/ml). Synechial adhesions may have led to traction on the iris and thus stimulated synthesis. The mere presence of vitreous in the anterior chamber (with or without corneal touch) did not substantially raise prostaglandin levels.

In our cases anterior inflammation as indicated by cells or flare or conjunctival injection was not associated with higher vitreous prostaglandin levels. In the one case of confirmed posterior segment inflammation (fungal endophthalmitis in an intravenous drug abuser) vitreous prostaglandins were only moderately elevated.

Of the two cases of cystoid macular oedema one had flagrant oedema associated with vitreous to the wound. Unfortunately this was one of the first specimens obtained, and it was diluted with BSS. In the second case the primary diagnosis was aphakic bullous keratopathy, but mild cystoid macular oedema had been demonstrated on a previous fluorescein angiogram. In both cases prostaglandins were undetectably low.

Discussion

Prostaglandins may well be involved in a variety of fundus disorders. Of all the pathological states in which these compounds are suspected, cystoid macular oedema is one of the most important. The evidence implicating prostaglandins in the aetiology of cystoid macular oedema is two-fold. First, an association between elevated aqueous prostaglandins and cystoid macular oedema has been shown. Miyake reported substantial amounts of PGE and $PGF_{2\alpha}$ (both at concentrations of approximately 13 000 pg/ml) in the aqueous of patients after cataract extraction.[5] Furthermore, he reported marked elevation of PGE and $PGF_{2\alpha}$ in the aqueous of nine eyes which had undergone intracapsular cataract extraction with vitreous loss, vitreous incarceration to the wound, and severe cystoid macular oedema.[12] After pars plana vitrectomy the levels were markedly reduced and fluorescein fundus angiography findings improved in five cases with relatively short duration cystoid macular oedema.

Earlier investigators had shown improvement in cystoid macular oedema by relieving vitreous incarceration to the wound. In the 1960s Iliff described a procedure to cut and remove vitreous strands that were anchored by adhesions to the cataract wound in patients with macular oedema. Vision improved in eight of his nine patients.[17] Gass and Norton noted inflammation in most eyes with formed vitreous to the wound and thus performed partial, open-sky anterior vitrectomies to reduce the inflammation and improve acuity. Of nine eyes so treated four remained unchanged, but five improved to 20/40 acuity or better within six months.[18] After the introduction of vitrectomy instruments Fung[19] and Federman *et al.*[20] each produced series of patients receiving vitrectomies for angiographically demonstrated cystoid macular oedema. Three quarters of their cases had at least a two-line improvement in acuity. Fung has summarised surgical therapy for chronic aphakic cystoid macular oedema and described the national, prospective, randomised, controlled study currently under way to assess the value of vitrectomy in this condition.[21]

These clinical demonstrations that resolving vitreous incarceration and mechanical iris irritation improves cystoid macular oedema are consistent with the hypothesis that such irritation produces a mediator which in turn produces cystoid macular oedema. That such a mediator is in fact involved, and that it is a prostaglandin, is not yet proved.

The second category of evidence implicating prostaglandins in cystoid macular oedema is the effect of prostaglandin inhibitors (like indomethacin) on the incidence of this condition. In Miyake's series of 25 cases of bilateral extraction of senile cataracts, topical indomethacin in one eye led to decreased incidence and severity of cystoid macular oedema compared with the fellow eye.[8] In Yannuzzi *et al.*'s series 100 patients undergoing cataract extraction received 1% topical indomethacin four times a day for four to six weeks and had significantly less aphakic cystoid macular oedema five weeks postoperatively (18% vs. 36% for controls), but there was no significant difference at 10 weeks.[10] In Klein *et al.*'s series five of 57 cataract patients who received oral indomethacin for four weeks developed cystoid macular oedema compared with 15 of 34 controls without indomethacin.[11] However, Yannuzzi *et al.* found no improvement in chronic cystoid macular oedema treated with oral indomethacin for three weeks.[22] Sholiton *et al.* did not find any significant difference in their series of 20 patients treated with oral indomethacin for six days (four patients developed cystoid macular oedema) and the control group (five of 22 developed cystoid macular oedema).[23] Jampol has recently reviewed the pharmacological prophylaxis and treatment of cystoid macular oedema.[6] The efficacy of a prostaglandin inhibitor has not yet been unequivocably proved.[24]

CONCLUSION

Prostaglandins in the vitreous cavity may well be significant in posterior segment disease. The evidence linking the compounds with aphakic cystoid macular oedema has been briefly reviewed. The values reported here indicate that prostaglandins are present in low levels in presumably normal vitreous. High levels seem to be associated with vitreous adhesions to iris. The two cases of cystoid macular oedema included here are insufficient to describe definitively the role vitreous prostaglandins play in this important disorder. Measurement of vitreous prostaglandins in additional cases of cystoid macular oedema will help resolve the question.

References

1 Eakins KE. Prostaglandin and non-prostaglandin mediated breakdown of the blood-aqueous barrier. *Exp Eye Res* 1977; **25** (suppl): 483–98.

2 Floman N, Zor U. Mechanism of steroid action in ocular inflammation: inhibition of prostaglandin production. *Invest Ophthalmol Visual Sci* 1977; **16**: 69–73.

3 Izawa Y, Masuda K. Estimation of prostaglandins by radioimmunoassay in rabbit aqueous humor after paracentesis. *Nippon Ganka Gakkai Zasshi* 1976; **80**: 448–51.

4 Sakata H. Argon laser photocoagulation to the pigmented rabbit iris: determination of the amount of prostaglandin E in aqueous humor after argon laser photocoagulation. *Folia Ophthalmol Jpn* 1978; **20**: 1378–81.

5 Miyake K. Prostaglandins as a causative factor of the cystoid macular edema after lens extraction. *Folia Ophthalmol Jpn* 1978; **29**: 447–50.

6 Jampol LM. Pharmacologic therapy of aphakic cystoid macular edema. *Ophthalmology* 1982; **89**: 891–7.

7 Miyake K. Prevention of cystoid macular oedema after lens extraction by topical indomethacin: a preliminary report. *Albrecht von Graefes Arch Klin Ophthalmol* 1977; **203**: 81–8.

8 Miyake K. Prevention of cystoid macular oedema after lens extraction by topical indomethacin. A control study in bilateral extractions. *Jpn J Ophthalmol* 1978; **22**: 85–94.

9 Miyake K, Sakamura S, Miura H. Long-term follow-up study on prevention of aphakic cystoid macular oedema by topical indomethacin. *Br J Ophthalmol* 1980; **64**: 324–8.

10 Yannuzzi LA, Landau AN, Turtz AI. Incidence of aphakic cystoid macular edema with the use of topical indomethacin. *Ophthalmology* 1981; **88**: 947–54.

11 Klein RM, Katzin HM, Yannuzzi LA. Effect of indomethacin pretreatment on aphakic cystoid macular edema. *Am J Ophthalmol* 1979; **87**: 487–9.

12 Miyake K, Sugiyama S, Norimatsu I, Ozawa T. Aqueous prostaglandins in persistent cystoid macular edema secondary to vitreous incarceration: effects of pars plana vitrectomy. *Jpn J Ophthalmol* 1980; **24**: 335–45.

13 Levine L. Levels of 13, 14-dihydro-15-Keto-PGE$_2$ in some biological fluids as measured by radio-immunoassay. *Prostaglandins* 1977; **14**: 1125–39.

14 Swartz SL, Williams GH, Hollenberg NK, Levine K, Dluhy RG, Moore TJ. Captopril-induced changes in prostaglandin production. *J Clin Invest* 1980; **65**: 1257–64.

15 Dzau VJ, Packer M, Lilly LS, Swartz SL, Hollenberg NK, Williams GH. Prostaglandins in severe congestive heart failure. *N Engl J Med* in press.

16 Rao GHR, Burris SM, Gerrard JM, White JG. Inhibition of prostaglandin synthesis in sheep vesicular microsomes by nitroblue tetrazolium and vitamin E. *Prostaglandins Med* 1979; **2**: 111–21.

17 Iliff CE. Treatment of the vitreous-tug syndrome. *Am J Ophthalmol* 1966; **62**: 856–9.

18 Gass JDM, Norton EWD. Follow-up study of cystoid macular edema following cataract extraction. *Trans Am Acad Ophthalmol Otolaryngol* 1969; **73**: 665–82.

19 Fung WE. Anterior vitrectomy for chronic aphakic cystoid macular edema. *Ophthalmology* 1980; **87**: 189–93.

20 Federman JL, Annesley WH Jr, Sarin LK, Remer P. Vitrectomy and cystoid macular edema. *Ophthalmology* 1980; **87**: 622–8.

21 Fung WE. Surgical therapy for chronic aphakic cystoid macular edema. *Ophthalmology* 1982; **89**: 898–901.

22 Yannuzzi LA, Klein RM, Wallyn RH, Cohen N, Katz I. Ineffectiveness of indomethacin in treatment of chronic cystoid macular edema. *Am J Ophthalmol* 1977; **84**: 517–9.

23 Sholiton DB, Reinhart WT, Frank KE. Indomethacin as a means of preventing cystoid macular edema following intracapsular cataract extraction. *Am Intra-Ocul Implant Soc J* 1979; **5**: 137–40.

24 Katz I. Indomethacin. *Ophthalmology* 1981; **88**: 455–8.

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Lipaemia retinalis in a 29-day-old infant with type 1 hyperlipoproteinaemia

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SUMMARY A 29-day-old infant born of consanguineous parents had type 1 hyperlipoproteinaemia associated with lipaemia retinalis. Biochemical analyses disclosed hypertriglyceridaemia, hyperchylomicronaemia, and lipoprotein lipase deficiency. Ophthalmoscopically all retinal vessels had the creamy appearance of lipaemia retinalis. The plasma lipoprotein levels and fundus condition became normal after her ingestion of fat was limited. To our knowledge this is the youngest patient reported with type 1 hyperlipoproteinaemia associated with lipaemia retinalis.

Type 1 hyperlipoproteinaemia is an autosomal recessively inherited disorder characterised by hyperchylomicronaemia and hypertriglyceridaemia.[1] To date fewer than 100 cases of the disorder have been reported.[2] Lipaemia retinalis is peculiar in this disorder.[1 2] However, the fundus picture has been rarely shown.[3] We describe lipaemia retinalis in a 29-day-old infant with type 1 hyperlipoproteinaemia.

Case report

An apparently normal baby was delivered on 12 July 1983 after a full-term uneventful pregnancy. Her birth weight was 3280 g. The parents, who were first cousins, and a 2-year-old brother were in good health (Fig. 1). The infant was breast-fed. When a blood sample was obtained from the cubital vein for newborn screening at 5 days of age, the patient's serum was observed to be milky. On 4 August she was referred to the Tohoku University Hospital for further examination.

Biochemical analyses disclosed a slightly elevated serum cholesterol level (400 mg/dl (10·4 mmol/l); normal, 130–250 mg/dl (3·4–6·5 mmol/l)) and a markedly increased serum triglyceride concentration (3000 mg/dl (33·9 mmol/l); normal, 35–130 mg/dl (0·4–1·5 mmol)). During the examination serum triglyceride level sometimes increased to 15000 mg/dl (169·5 mmol/l). The serum phospholipid level was within normal range. The presence of hyperchylomicronaemia was demonstrated by agar-gel electrophoresis. Apolipoprotein CII assayed by immunodiffusion was normal. Lipoprotein lipase activity in postheparin plasma examined by the method of Murase and associates,[4] based on immunoprecipitation of hepatic triglyceride lipase, was negligible. The deficiency of lipoprotein lipase was thus confirmed in this case. Other laboratory data, including blood cell counts, electrolytes, liver function tests, estimations of glucose, ammonia, and amylase, and immunoelectrophoresis, were normal. The liver and spleen were not enlarged.

At 29 days of age an ophthalmic examination was performed. A few lipid depositions, or eruptive xanthoma, were noted in the upper eye lids. Ocular tension was normal to palpation. Pupils were isocoric

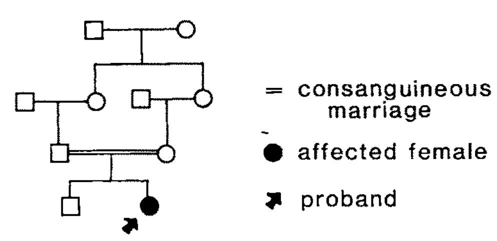

Fig. 1 *Pedigree.*

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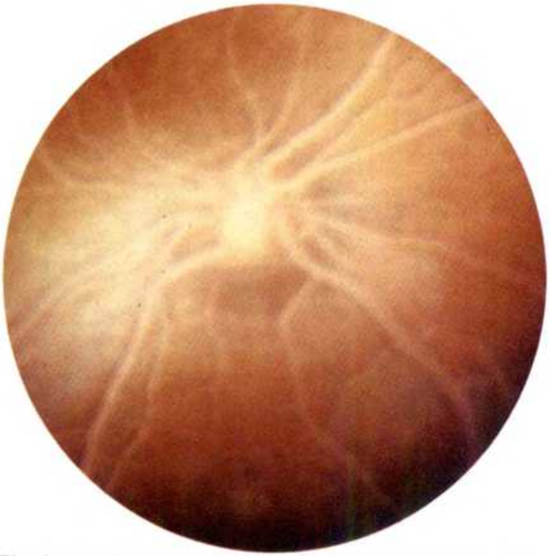

Fig. 2 *Fundus photograph of left eye of proband shows the whitish optic disc and creamy retinal vessels, i.e. lipaemia retinalis.*

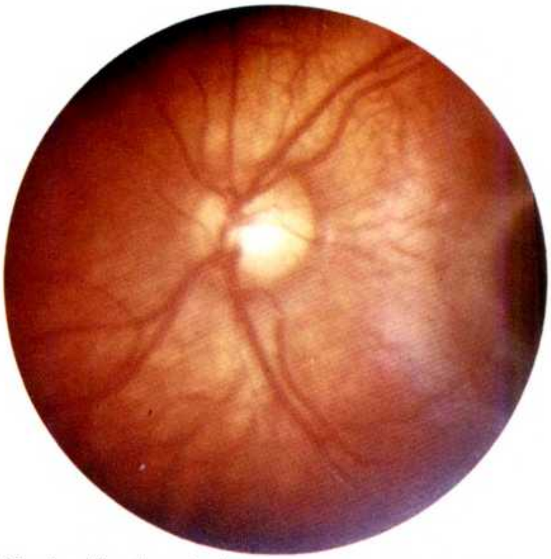

Fig. 3 *After the patient's ingestion of fat was stringently limited, the fundus changes cleared.*

and reactive. The corneas were transparent, and corneal arcus or crystalline was absent. Xanthoma was not seen in the iris. The optical media was clear.

Ophthalmoscopically the optic discs were whitish but not swollen. All vessels had a creamy appearance, and it was difficult to differentiate retinal arterioles from veins (Fig. 2). The extravasation of lipid material from the vessels was not prominent. The retina seemed normal, and no retinal haemorrhage was noted. The scotopic electroretinogram response was normal.

After the patient's ingestion of fat was stringently limited, serum cholesterol, triglyceride, and chylomicron levels were reduced: serum cholesterol, 200 mg/dl (5·2 mmol/l); triglyceride, 300 mg/dl (3·4 mmol/l); and chylomicron, normal levels within several days. When the triglyceride concentration dropped below about 2500 mg/dl (28·2 mmol/l), the fundus changes cleared (Fig. 3). The eruptive xanthoma disappeared thereafter.

Discussion

Lipaemia retinalis is a manifestation of excess triglyceride in the bloodstream: the retinal vessels are found to be milky or creamy when triglyceride levels rise to 2000 to 2500 mg/dl (22·6 to 28·2 mmol/l) or greater.[2] Lipaemia is seen not only in retinal vessels but also in limbal vessels.[5] Lipaemia retinalis has been graded 0 to III by Vinger and Sachs.[6] Fundus changes in our case were grade III according to this classification. Increased cholesterol levels alone do not cause the milky plasma.[2]

Lipaemia retinalis is reported in cases of types I, II, IV, and V hyperlipoproteinaemia.[3] Type I hyperlipoproteinaemia is characterised by hyperchylomicronaemia and hypertriglyceridaemia and confirmed by lipoprotein lipase deficiency.[2] The plasma lipoprotein levels and fundus condition usually respond to treatment with a low-fat diet, as in our case.

Fundus photographs of lipaemia retinalis have been shown mostly for type V hyperlipoproteinaemia secondary to diabetes.[6 7] The fundus picture is not found in cases of idiopathic or retention (former name of type I) hyperlipaemia,[8 9] and has been found only in 18- and 28-year-old men with type I hyperlipoproteinaemia.[1 10] Type I hyperlipoproteinaemia in an 8-day-old infant has been reported, but she lacked eruptive xanthoma and lipaemia retinalis.[11] To our knowledge our present case is the youngest patient with type I hyperlipoproteinaemia associated with lipaemia retinalis.

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References

1 Nikkilä EA. Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS, eds. *Metabolic basis of inherited diseases*. 5th ed. New York: McGraw-Hill, 1983: 622–42.

2 Winder AF. Disorders of lipid and lipoprotein metabolism. In: Garner A, Klintworth GK, eds. *Pathobiology of ocular disease.* New York: Dekker, 1982: 1047–75.

3 Spaeth GL. Inborn errors of metabolism affecting the eye. In: Harley R, ed. *Pediatric ophthalmology.* 2nd ed. Philadelphia: Sanders, 1983; **2:** 1070–143.

4 Murase T, Yamada N, Ohsawa N, Kosaka K, Morita S, Yoshida S. Decline of postheparin plasma lipoprotein lipase in acromegalic patients. *Metabolism* 1980; **29:** 666–72.

5 Bron AJ, Williams HP. Lipaemia of the limbal vessels. *Br J Ophthalmol* 1972; **56:** 343–6.

6 Vinger PF, Sachs BA. Ocular manifestation of hyperlipoproteinaemia. *Am J Ophthalmol* 1970; **70:** 563–73.

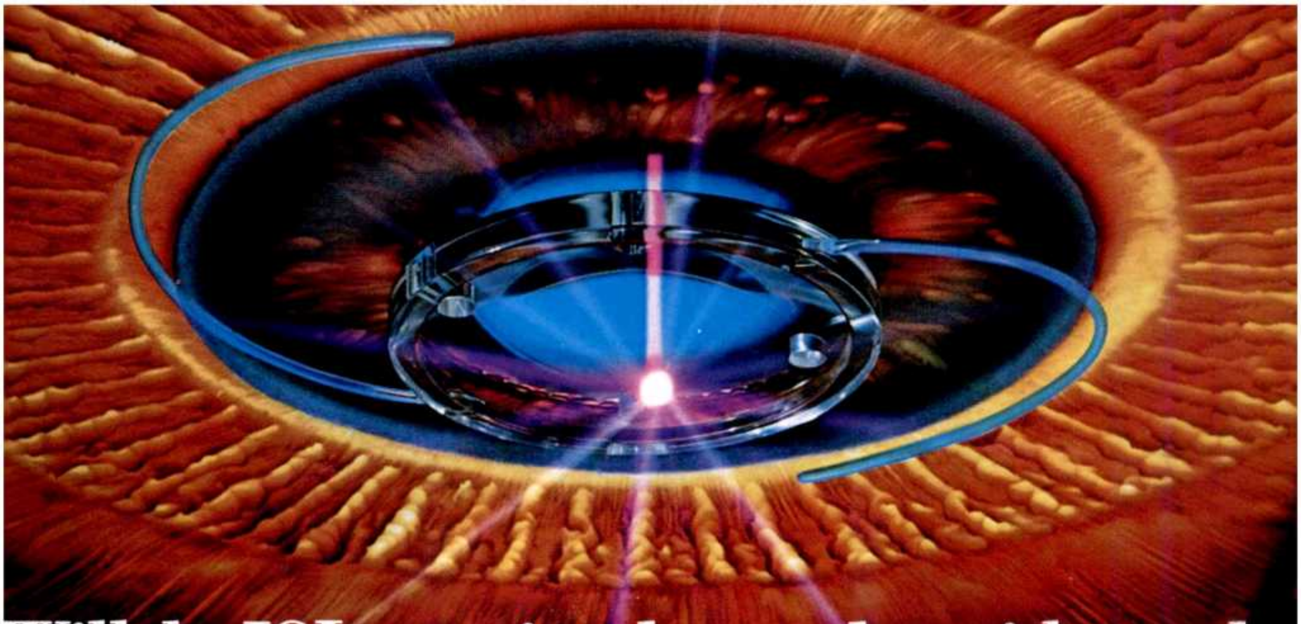
7 Kurz GH, Shakib M, Sohmer KK, Friedman AH. The retina in type 5 hyperlipoproteinaemia. *Am J Ophthalmol* 1976; **82:** 32–43.

8 Dunphy EB. Ocular conditions associated with idiopathic hyperlipemia. *Am J Ophthalmol* 1950; **33:** 1579–86.

9 Davies WS. Idiopathic lipemia retinalis. *Arch Ophthalmol* 1955; **53:** 105–8.

10 Spaeth GL. Ocular manifestations of lipoprotein disease. *J Cont Educ Ophthalmol* 1979; **41:** 11–24.

11 Sadon N, Drucker MM, Arber I, Joseph D, Franco S, Shapiro MS. Type I hyperlipoproteinaemia in an 8-year-old infant. *J Pediatr* 1977; **90:** 775–77.



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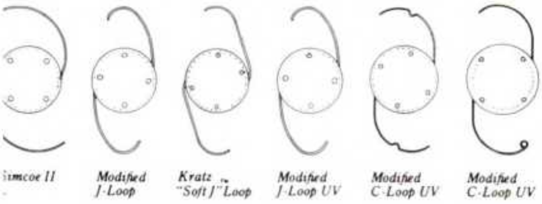

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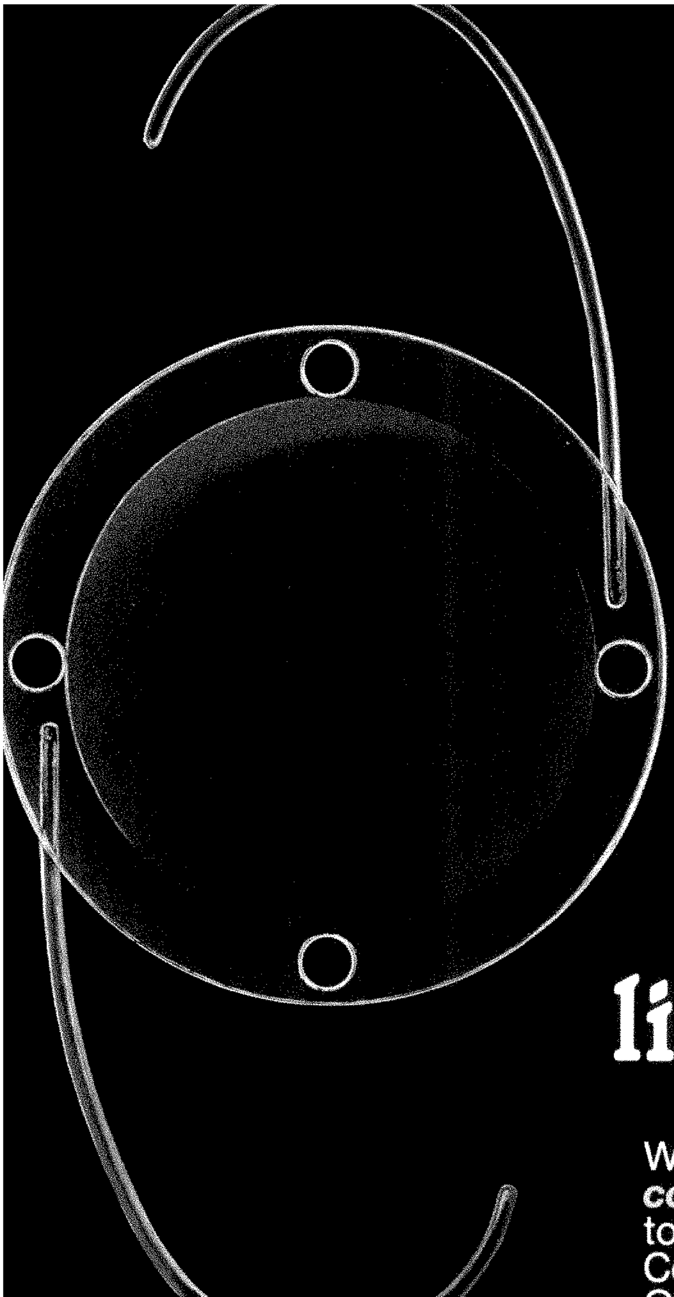

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Clinical trials of vitamin B_6 and proline supplementation for gyrate atrophy of the choroid and retina

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SUMMARY Five patients with gyrate atrophy of the choroid and retina were examined ophthalmologically, especially ophthalmoscopically, to evaluate trials of vitamin B_6 (pyridoxine) or supplementary proline. The oral administration of vitamin B_6 was tried in two patients. The vitamin did not alter the serum ornithine level and the progression of chorioretinal atrophy in one patient (case 2). Despite a reduced serum ornithine level following vitamin B_6 administration, chorioretinal atrophy progressed gradually in another patient (case 3). Supplementary proline was tried in four patients. Despite the supplementation the serum proline level did not increase, and the chorioretinal atrophy progressed in one patient (case 2) who received both vitamin B_6 and proline. Supplementary proline minimised the progression of gyrate atrophy in the youngest patient (case 1) and halted the progression in two others (cases 4 and 5). Supplementary proline may possibly lessen the progression of chorioretinal lesions in gyrate atrophy.

Gyrate atrophy of the choroid and retina is known in association with hyperornithinaemia.[1] Although a deficiency of ornithine-ketoacid-transaminase (OKT) was found to cause the disorder,[1-5] the pathogenic mechanism responsible for the chorioretinal lesion is still obscure, as is a generally accepted management of the disease. To date three major trials for the management of gyrate atrophy have been reported[6]: (1) pyridoxine or vitamin B_6,[7 8] (2) low-protein and arginine-restricted diets,[9-12] and (3) creatine.[13]

We tried vitamin B_6 (pyridoxine) administration in vitamin B_6-responsive (case 3) and non-responsive (case 2) patients, and proline supplementation in vitamin B_6-non-responsive patients (cases 1, 2, 4, and 5). Biochemical parameters (serum amino acid levels) and visual function tests (visual acuity, visual field, dark adaptation, electroretinogram, and colour sense) were mainly examined to evaluate the trials in a manner similar to that described by others.[8 9 11] The slow progression of sharply defined chorioretinal atrophic lesions is most characteristic in this disorder. We therefore compared the extent of sharply defined lesions before and after our trials.

Material and methods

Ocular manifestations and biochemical abnormalities of the cases presented here have been previously reported in part elsewhere.[14-16] The daily doses of proline and/or vitamin B_6 were divided into three equal parts, given orally at 7.00 am, 12.00 am, and 5.30 pm.

Blood samples were drawn usually between 6.30 and 8.00 am after 10 hours of fasting. Serum was separated, and the amino acid concentration was estimated with an amino acid analyser (Hitachi 835). Fasting serum amino acids were examined every four or six months, and the mean values are shown in the tables.

The electroretinograms, electro-oculograms, fundus photographs, visual fields (Goldmann perimeter), and dark adaptations (Goldmann-Weeker instrument) were recorded with the same equipment and techniques throughout the study, as previously reported.[14-16]

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Table 1 *Serum amino acid levels, treatment, and ophthalmic findings in case 1*

	Age (years)						
	2	*4*	*5*	*6*	*7*	*8*	*9*
Serum amino acids (mg/dl)*							
Ornithine (normal 0·36–1·56)	8·48	9·76	10·72	8·84	11·93	10·05	9·05
Lysine (normal 1·49–2·97)	1·06	0·97	1·26	1·04	1·35	1·40	1·21
Proline (normal 0·82–2·50)	1·30	1·86	4·31	3·72	3·62	4·52	4·81
Treatment							
Vitamin B_6		150 mg ——→					
Proline		2 g ——→	3 g ——→	5 g ——→	10 g ——→	——→	
Ophthalmic findings							
Visual acuity (OU)		0·3	0·3	0·7	1·0	1·0	1·0
Refraction (OU)		−2 D	−1·5 D	−1·5 D	−1·0 D	−1·0 D	−1·0 D
Fundus	Normal in appearance	Yellow-white spots	——→	Increased slightly in size and number			
ERG		Subnormal (nearly extinct)		Almost extinct			

*SI conversion: amino acid (nitrogen) mg/dl×0·714=mmol/l.

Case reports

CASE 1

This was a boy born on 18 April 1975. His case has been briefly described previously up to the age of 5 years.[14] He received vitamin B_6 150 mg/day for one year, and proline for five years (2 g/day for 1 year, 3 g/day for 1 year, 5 g/day for 1 year, and 10 g/day for 2 years). His body weight was 13·5 kg at age 5 and 20·5 kg at age 8. The serum amino acid levels and ophthalmic findings are given in Table 1. During proline supplementation the serum ornithine level was unchanged, and the serum proline level was above normal (Fig. 1). Visual acuity increased from 0·3 to 1·0 OU, and the refractive error lessened gradually from −2 D to −1 D. Yellowish-white spots in the peripheral fundus seemed to increase only minimally in size and number (Fig. 2). The ERG showed a only slight deterioration.

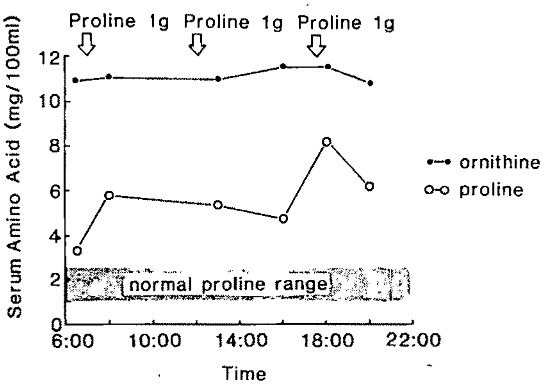

Fig. 1 *Diurnal profile of ornithine and proline levels during proline supplementation in case 1 at the age of 5 years. SI conversion: amino acid (nitrogen) mg*dl×0·714=mmol/l.*

CASE 2

This was a boy born on 23 July 1971. His case has been described briefly up to the age of 8 years.[14] He had received both vitamin B_6 120 mg/day and proline 2 to 3 g/day. His body weight was 21·5 kg at age 8 and 27 kg at age 11. The serum levels of amino acids and ophthalmic findings are presented in Table 2. Despite the proline supplementation the serum proline level was within the normal range. Hyperornithinaemia did not improve.

At the age of 9 years he had a vitreous haemorrhage in the left eye, which gradually cleared. One year later an intraocular haemorrhage was noted in the right eye, which did not disappear in spite of haemostatic drug therapy. Chorioretinal lesions markedly progressed in size and number despite vitamin B_6 and proline therapy (Fig. 3).

CASE 3

A brief case report described this boy, born on 1 February 1962, up to the age of 17 years.[14] He received vitamin B_6 600 mg/day. His body weight was 44 kg at age 17. The serum amino acid levels and ophthalmic findings are shown in Table 3. After the vitamin administration the serum ornithine levels fell markedly but did not reach the normal range. Treatment with high doses of vitamin B_6 produced no improvement in the visual fields or EOG. The visual acuity, dark adaptation, and ERG deteriorated. Chorioretinal lesions enlarged in size despite large amounts of the vitamin (Fig. 4).

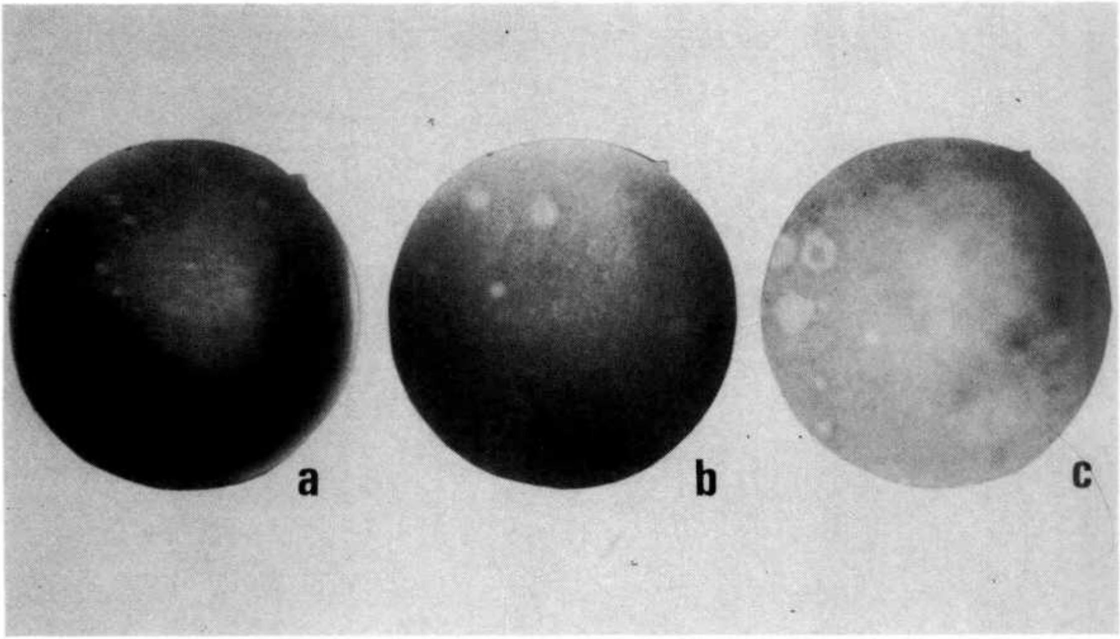

Fig. 2 *Chorioretinal atrophies in case 1:* (a) *at the age of 4 years,*[14] (b) *at age 6, and* (c) *at age 9. Chorioretinal atrophic lesions in the midperiphery at age 9 are small in size (one-third disc diameter) and few in number.*

CASE 4

A brief report described the case of this man, born on 10 October 1956, up to the age of 23 years.[15] He received proline 3 g/day. His body weight was 47 kg at age 23. The serum amino acid levels and ophthalmic findings are given in Table 4. The high level of serum

Table 2 *Serum amino acid levels, treatment, and ophthalmic findings of case 2*

		Age (years)				
		5	*8*	*9*	*10*	*11*
Serum amino acids (mg/dl)*						
Ornithine (normal 0·35–1·56)			12·95	10·56	11·34	14·42
Lysine (normal 1·49–2·97)			1·49	1·00	1·18	1·13
Proline (normal 0·82–2·50)			0·95	1·65	2·19	2·11
Treatment						
Vitamin B_6			120 mg →	→	→	→
Proline			2 g →	→	→ 3 g →	→
Hemostatic drugs				→	→	→
Ophthalmic findings						
Visual acuity	OD	0·4	0·4	0·4	0·1	LS
	OS	0·4	0·4	0·2	HM	0·2
Refraction	OD	−5 D	−9 D	−9 D	−10 D	
	OS	−5 D	−10 D	−10 D		−10 D
Fundus	OD	Sharply defined atrophy		Vitreous haemorrhage →	Vitreous opacity	
	OS	Sharply defined atrophy		Vitreous haemorrhage	Atrophy markedly increased	
Visual field (V 4)	OD	<40°		<30°		
	OS	<40°		<30°		
ERG		Subnormal		Almost extinct		
EOG		Flat		Flat		

*SI conversion: amino acid (nitrogen) mg/dl×0·714=mmol/l.

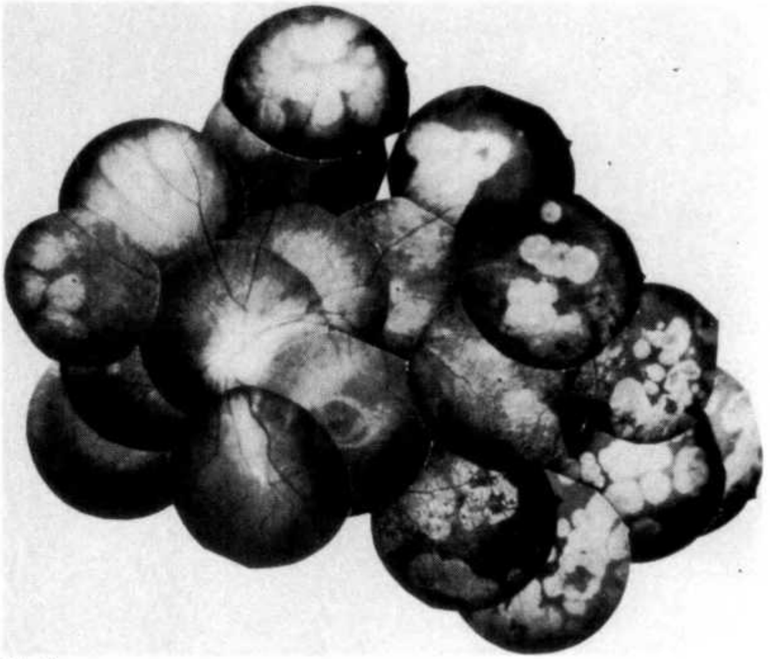

Fig. 3a

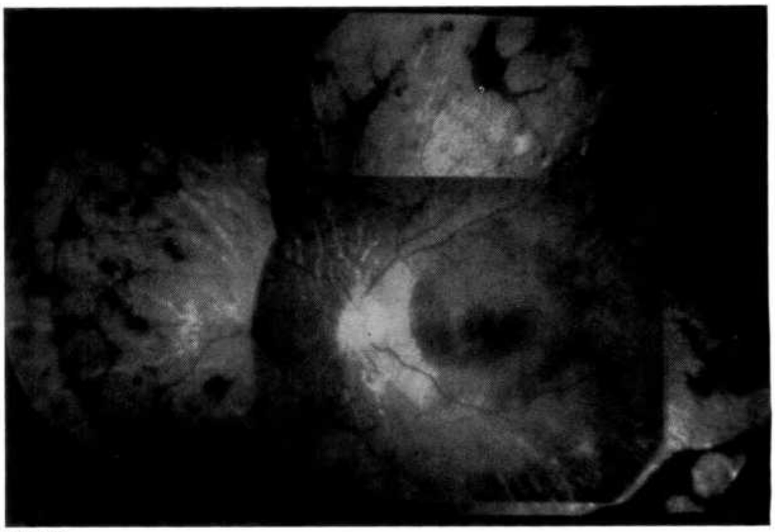

Fig. 3b

Fig. 3 *Left fundus photographs of case 2:* (a) *at the age of 8 years,*[14] *and* (b) *at age 11. Chorioretinal lesions approach the posterior pole. Progression of the atrophy is remarkable.*

ornithine remained unchanged, and the proline level increased after proline supplementation. Visual acuity decreased minimally, accompanied by the slight progression of a posterior subcapsular cataract. The region of chorioretinal atrophy remained unchanged in size for 24 months (Fig. 5).

CASE 5

The case of this woman, born on 5 November 1949, has been briefly reported on previously up to the age of 32 years.[16] She received proline 3 g/day. Her body weight was 47 kg at age 32. The serum amino acid level and ophthalmic findings are shown in Table 5. The high level of serum ornithine did not decrease, but the proline level increased after proline supplementation. Visual acuity, visual fields, dark adaptation, ERG, EOG, and areas of chorioretinal atrophy remained unchanged.

Table 3 *Serum amino acid levels, treatment, and ophthalmic findings of case 3*

		Age (years)			
		17	*18*	*19*	*20*
Serum amino acids (mg/dl)					
Ornithine (normal 0·36–1·56)		6·92	3·05	2·78	3·75
Lysine (normal 1·49–2·97)		2·15	2·00	2·35	2·18
Proline (normal 0·82–2·50)		2·87	2·41	2·72	2·44
Treatment					
Vitamin B_6		600 mg →			
Ophthalmic findings					
Visual acuity	OD	0·03		0·03	0·03
	OS	0·6		0·06	0·04
Refraction	OD	−13 D		−13 D	
	OS	−14 D		−14 D	
Fundus	OU	Chorioretinal atrophies	→	Gradually increased	
Dark adaptation		Biphasic		Monophasic	
ERG		Subnormal		Subnormal (nearly extinct)	
EOG		Flat		Flat	
Visual field (V 4)	OD	<10°		<10°	
	OS	<20°		<20°	

SI conversion: amino acid (nitrogen) mg/dl×0·714=mmol/l.

Discussion

We evaluated trials of vitamin B_6 (pyridoxine) and supplementary proline for gyrate atrophy. The biochemical basis for the vitamin B_6 trial was as follows. We previously reported on a patient (case 3) who was vitamin B_6-responsive and whose serum ornithine level decreased to a maximum of 60% after the vitamin therapy (600 mg/day).[14] The vitamin partially activates the activity of OKT and is expected to halt the progression of the chorioretinal atrophy. Vitamin B_6 was tried in a B_6-non-responsive patient (case 3) as well.

The biochemical basis for the proline supplementation was as follows. We found (1) a disturbance of de-novo formation of proline in affected patients.[17]

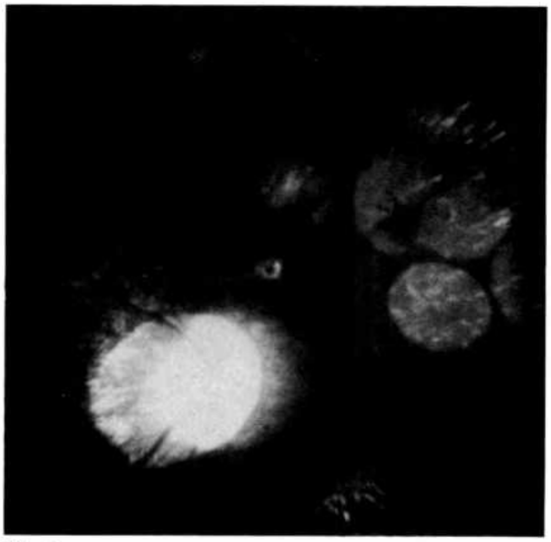

Fig. 4a

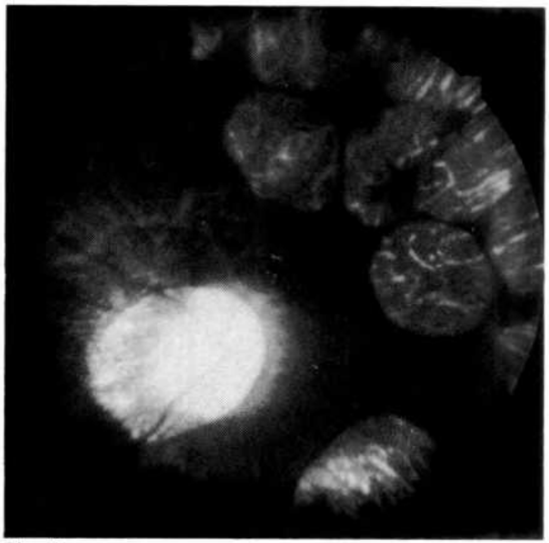

Fig. 4b

Fig. 4 *Chorioretinal atrophy of case 3:* (a) *right eye at age 17 years;* (b) *same region as in (a) at age 19 shows enlargement of the atrophic area.*

Table 4 *Serum amino acid levels, treatment, and ophthalmic findings of case 4*

		Age (years)			
		23	*24*	*25*	*26*
Serum amino acids (mg/dl)*					
Ornithine (normal 0·36–1·56)		13·01	13·05	15·03	12·45
Lysine (normal 1·49–2·97)		1·60	1·50	1·56	1·49
Proline (normal 0·82–2·50)		1·97	2·55	3·21	3·44
Treatment					
Proline		3 g →			
Ophthalmic findings					
Visual acuity	OD	0·1		0·08	0·08
	OS	0·08		0·07	0·06
Refraction	OD	−14 D		−14 D	
	OS	−13 D		−13 D	
Lens		Cataract		Cataract (slightly progressed)	
Fundus		Gyrate atrophy		Gyrate atrophy (unchanged)	
Dark adaptation		Monophasic		Monophasic	
Visual field (V 4)		10°		10°	
ERG		Extinct		Extinct	
EOG		Flat		Flat	

*SI conversion: amino acid (nitrogen) mg/dl×0·714=mmol/l.

Serum proline increased after oral loading of ornithine in normal controls, whereas the proline in the patients did not increase. (2) The OKT activity was high in the retina and choroid, particularly in the retinal pigment epithelium, in bovine and human eyes.[18,19] The retinal pigment epithelium and neuroretina lack proline oxidase activity[20]; Δ^1-pyrroline-5-carboxylate dehydrogenase activity is low in the retina[20]; and Δ^1-pyrroline-5-carboxylate reductase activity is high in the retina and choroid.[20] Ornithine in the retina may be converted into proline by the cooperative action of OKT and Δ^1-pyrroline-5-carboxylate reductase.[20] Furthermore, the importance of ornithine as a precursor for proline in mammalian cells has been proposed by others.[21] The intraocularly injected radioisotope-labelled ornithine

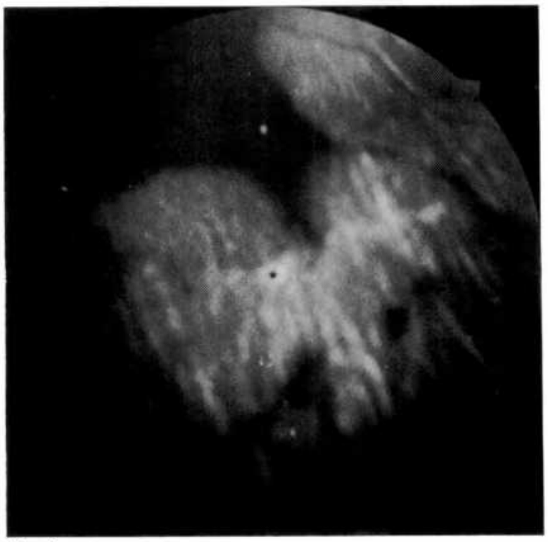

Fig. 5a

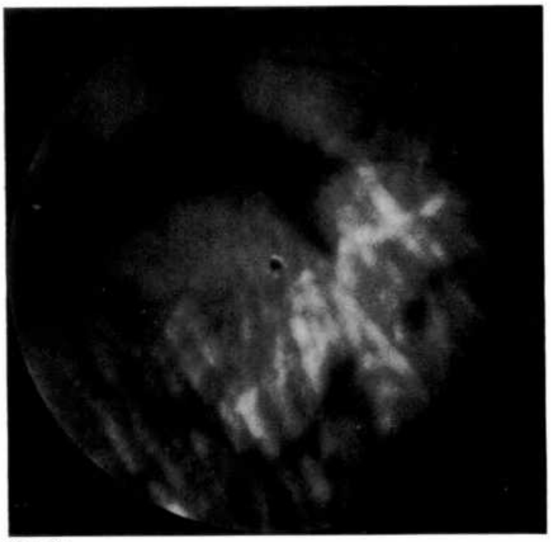

Fig. 5b

Fig. 5 *Chorioretinal atrophy in case 4:* (a) *at the age 23;* (b) *same region as in (a) at age 25 years. No progression of chorioretinal atrophy is photographically documented after a two-year interval with proline supplementation.*

Table 5 *Serum amino acid levels, treatment, and ophthalmic findings of case 5*

		Age (years)		
		32	*33*	*34*
Serum amino acids (mg/dl)*				
Ornithine (normal 0·36–1·56)		11·27	15·08	13·08
Lysine (normal 1·49–2·97)		1·11	1·23	1·20
Proline (normal 0·82–2·50)		1·75	3·45	3·18
Treatment				
Proline		3 g →	→	→
Ophthalmic findings				
Visual acuity	OD	0·1	0·1	0·1
	OS	0·1	0·1	0·1
Refraction	OD	+5·25 D	+5·25 D	+5·25D
	OS	−12 D	−12 D	−12 D
Lens	OD	Aphakia	Aphakia	
	OS	Cataract	Cataract	
Fundus		Gyrate atrophy	Gyrate atrophy	
Dark adaptation		Monophasic	Monophasic	
ERG		Extinct	Extinct	
EOG		Flat	Flat	Flat
Visual field (V 4)		<10°	<10°	<10°

*SI conversion: amino acid (nitrogen) mg/dl×0·714=mmol/l.

was incorporated mainly into I-III type, IV type, and V type collagens via proline (Matsuzawa T, Iwasaki K, Mishima K, Takahashi H, unpublished data). (3) Atypical gyrate atrophy without hyperornithinaemia has been found.[22] Our patient showed a fundus appearance similar to that of gyrate atrophy.[22] Another unrelated patient with atypical gyrate atrophy and prolinuria was found (Hirata S, Mishima H, Baba S, Choshi K, unpublished data). Prolinuria (iminoglycinuria), probably caused by transport defects of proline, hydroxyproline, and glycine, was noted in these patients. (4) The patients with hyperornithinaemia - hyperammonaemia - homocitrullinuria (H-H-H syndrome) had no retinochoroidal lesions.[6 23] The H-H-H syndrome suggests that hyperornithinaemia is not causative in the retinochoroidal lesions.

The above data strongly suggest that a deficiency of proline in the retina and choroid may produce atrophies in affected patients despite normal serum proline levels. Supplementary proline, therefore, is supposed to diffuse into the tissues and halt the progression of the atrophy.

In case 1 the visual acuity did improve after supplementary proline, and the refractive error lessened. Although myopic changes with age are usually noted in this disorder, the refractive error lessened in case 1. Yellowish white spots in the peripheral fundus seemed to increase only minimally, and the deterioration of ERG response was only slight. At age 9 years the chorioretinal lesions were much smaller and fewer than those in patients of the same or younger ages who received no proline supplementation.[14 24–26]

The serum proline level in case 2 did not increase despite the vitamin B_6 and supplementary proline, and the hyperornithinaemia was not improved. A marked progression of chorioretinal atrophy and vitreous haemorrhage was observed.

In case 3 the daily dose of 600 mg vitamin B_6 induced the maximal reduction of the serum ornithine level: the higher dose over 600 mg vitamin B_6 could not reduce the ornithine level to normal range. Despite a reduced ornithine level after vitamin B_6 therapy areas of chorioretinal atrophy enlarged. His poor visual acuity in the light eye was thought to be amblyopia.

In case 4 the posterior subcapsular cataract progressed slightly despite the supplementary proline. Regions of chorioretinal atrophy were probably unchanged. In case 5 visual functions and chorioretinal atrophic areas did not change during the trial of supplementary proline.

Vitreous haemorrhage can occur in association with the disorder.[16] Therefore it is unlikely that the haemorrhage in case 2 is a complication of supplementary proline. No obvious complication associated with the supplementary proline was observed, suggesting that hyperprolinaemia is probably harmless.[27] Giordano and associates[28] proposed the efficacy of lysine supplementation in gyrate atrophy, but visual improvement was not described. Serum lysine levels in all our cases were below normal range and did not change during proline supplementation.

Although the natural progression of the disease is not well known, acuities in phakic eyes tend to decrease from 20/30 to 20/200 in 10 years or less, and constriction of visual fields with age is marked.[29] Takki and Milton[29] reported no clinical correlation between the extent of chorioretinal atrophy and age except in patients younger than 13–15 years. Therefore the extent and progression of the atrophy in our cases 1 and 2 are suitable for evaluating the trials. After proline supplementation the chorioretinal lesions progressed only minimally in case 1. Despite the supplementation of the vitamin and proline, the serum proline level did not increase and the chorioretinal atrophy progressed in case 2. We conclude (1) that vitamin B_6 does not halt the progression of chorioretinal atrophy in these patients, even if the serum ornithine level is reduced after vitamin supplementation, and (2) that the supplementary proline may minimise the progression of chorioretinal atrophy.

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References

1 Simell O, Takki K. Raised plasma-ornithine and gyrate atrophy of the choroid and retina. *Lancet* 1973; **i**: 1031–3.

2 Senger RCA, Trijbels JMF, Brussaard JH, Deutman AF. Gyrate atrophy of the choroid and retina and ornithine-ketoacid-aminotransferase deficiency. *Pediatr Res* 1976; **10**: 894.

3 Shih VE, Berson EL, Mandell R, Schmidt SY. Ornithine ketoacid transaminase deficiency gyrate atrophy of the choroid and retina. *Am J Hum Genet* 1978; **30**: 174–9.

4 Kaiser-Kupfer MI, Valle D, Del Valle LA. A specific enzyme defect in gyrate atrophy. *Am J Ophthalmol* 1978; **85**: 200–4.

5 O'Donnell JJ, Sandman RP, Martin SR. Gyrate atrophy of the retina. Inborn error of L-ornithine; 2-oxoacid aminotransferase. *Science* 1978; **200**: 200–1.

6 Valle D, Simell O. The hyperornithinemias. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, Goldstein JL, Brown MS, eds. *The metabolic basis of inherited disease.* 5th ed. New York: McGran-Hill, 1983: 382–401.

7 Weleber RG, Kennaway NG, Buist NR. Vitamin B_6 in management of gyrate atrophy of choroid and retina. *Lancet* 1978; **ii**: 1213.

8 Weleber RG, Kennaway NG. Clinical trials of vitamin B_6 for gyrate atrophy of the choroid and retina. *Ophthalmology* 1981; **88**: 316–24.

9 Kaiser-Kupfer MI, De Monasterio F, Valle D, Walser M, Brusilow SW. Visual results of a long-term trial of a low-arginine diet in gyrate atrophy of the choroid and retina. *Ophthalmology* 1981; **88**: 307–10.

10 Berson E, Shih V, Sullivan PL. Ocular findings in patients with gyrate atrophy on pyridoxine and low-protein, low-arginine diets. *Ophthalmology* 1981; **88**: 311–5.

11 Valle D, Walser M, Brusilow S, Kaiser-Kupfer MI, Takki K. Gyrate atrophy of the choroid and retina. Biochemical considerations and experience with an arginine-restricted diet. *Ophthalmology* 1981; **88**: 325–30.

12 McInnes RR, Arshinoff SA, Bell L, Marliss EB, McCulloch JC. Hyperornithinaemia and gyrate atrophy of the retina. Improvement of vision during treatment with a low-arginine diet. *Lancet* 1981; **i**: 513–7.

13 Sipilä I, Rapola J, Simell O, Vannas A. Supplementary creatine as a treatment for gyrate atrophy of the choroid and retina. *N Engl J Med* 1981; **304**: 867–70.

14 Hayasaka S, Saito T, Nakajima H, *et al.* Gyrate atrophy with hyperornithinaemia. Different types of responsiveness to vitamin B_6. *Br J Ophthalmol* 1981; **65**: 478–83.

15 Nakajima H, Hayasaka S, Shiono T, *et al.* A case of gyrate atrophy of the choroid and retina associated with hyperornithinemia. *Jpn J Ophthalmol* 1981; **25**: 495–500.

16 Takahashi O, Hayasaka S, Kiyosawa M, *et al.* Gyrate atrophy of the choroid and retina. A case report. *Folia Ophthalmol Jpn* 1983; **34**: 2661–4.

17 Saito T, Omura K, Hayasaka S, *et al.* Hyperornithinemia with gyrate atrophy of the choroid and retina. A disturbance in de novo formation of proline. *Tohoku J Exp Med* 1981; **135**: 395–402.

18 Hayasaka S, Shiono T, Takaku Y, Mizuno K. Ornithine ketoacid transaminase in the bovine eye. *Invest Ophthalmol Visual Sci* 1980; **19**: 1457–60.

19 Shiono T, Hayasaka S, Mizuno K. Presence of ornithine ketoacid aminotransferase in human ocular tissues. *Albrecht von Graefes Arch Klin Ophthalmol* 1982; **218**: 34–36.

20 Hayasaka S, Matsuzawa T, Shiono T, Mizuno K, Ishiguro I. Enzymes metabolizing ornithine-proline pathway in the bovine eye. *Exp Eye Res* 1982; **34**: 635–8.

21 Smith RJ, Phang MM. The importance of ornithine as a precursor for proline in mammalian cells. *J Cell Physiol* 1979; **98**: 475–82.

22 Hayasaka S, Mizuno K, Yabata K, Saito T, Tada K. Atypical gyrate atrophy of the choroid and retina associated with iminoglycinuria. *Arch Ophthalmol* 1982; **100**: 423–5.

23 Shih VE, Efron ML, Moser HW. Hyperornithinemia, hyperammonemia and homocitrullinemia. A new disorder of amino acid metabolism associated with myoclonic seizures and mental retardation. *Am J Dis Child* 1969; **117**: 83–92.

24 Rinaldi E, Stoppoloni GP, Savastano S, Russo S, Cotticelli L. Gyrate atrophy of choroid associated with hyperornithinemia. Report of first case in Italy. *J Pediatr Ophthalmol* 1979; **16**: 133–5.

25 Hodes DT, Oberholzer VG, Mushin AS, Briddon A, Laurence BM. Hyperornithinaemia with gyrate atrophy of the choroid and retina in two siblings. *J R Soc Med* 1980; **73**: 588–91.

26 Takki K, Simell O. Gyrate atrophy of the choroid and retina with hyperornithinemia (HOGA). *Birth Defects* 1976; **12**: 372–84.

27 Rosenberg LE, Scriver CR. Disorders of imino acid metabolism. In: Bondy PK, Rosenberg LE, eds. *Metabolic control and disease.* 8th ed. Philadelphia: Saunders, 1980: 654–60.

28 Giordano C, De Santo NG, Pluvio M, Santinelli R, Stoppoloni G. Lysine in treatment of hyperornithinemia. *Nephron* 1978; **22**: 97–106.

29 Takki KK, Milton RC. The natural history of gyrate atrophy of the choroid and retina. *Ophthalmology* 1980; **88**: 292–301.

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Xenon arc photocoagulation for treatment of subluxation of lens

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SUMMARY In the treatment of congenital or acquired subluxation of the lens a conservative approach to reposition the pupil in front of the aphakic area by the use of the xenon arc photocoagulator is emphasised. The management of two cases of subluxation is discussed in detail and the results evaluated. The ease of repositioning the pupil by means of iris photocoagulation and the absence of surgical complications are indications for the use of this non-invasive procedure in the treatment of subluxated lenses.

Subluxation of the lens, congenital or acquired, results in disturbance of vision for various reasons such as uncorrectable lenticular astigmatism, lens opacifications, or the complications of subluxation itself. Uncomplicated subluxation occurs especially in younger people, and when the lens is clear it is usually treated conservatively. The indications for surgical intervention and the choice of procedure are still a matter of controversy.

Surgical techniques previously used in the management of subluxated lenses include iridectomy, discission, aspiration and lens extraction with forceps, and vectis or cryo extraction. Despite recent advances in surgical techniques and skills, the removal of the lens is fraught with a high incidence of operative and postoperative complications[1] [2] such as vitreous loss, retinal detachment, glaucoma, and intraocular infection. Opening up of the globe to perform an optical iridectomy also has the same disadvantages. Straatsma *et al.*[3] were the first to carry out iris photocoagulation for improving the visual acuity in cases of subluxation of lens by utilising the aphakic optical system. Peyman *et al.*[4] treated 10 eyes with subluxation of the soft lens by the vitrophage, with satisfactory improvement in vision. We now report the results of two such cases managed by iris photocoagulation to reposition the pupil so as to increase the aphakic pupillary zone.

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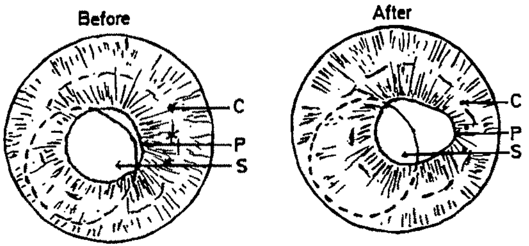

Fig. 1 *Before and after coagulation of the iris with xenon arc. P=pupillary border. S=subluxated lens. C=site of coagulation.*

Material and methods

A xenon arc photocoagulator Clinitex Log 3 was used. Fig. 1 illustrates the principle and the site of iris which is recommended for photocoagulation. This must avoid damage to the sphincter pupillae muscle. The energy to be delivered to iris tissue is minimal and does not produce any iritis. The increased cellularity of the aqueous can be effectively controlled in 24–48 hours with local corticosteroid drops.

Case reports

CASE 1

A 29-year-old woman attended the Ophthalmology Outpatient Department of Jipmer Hospital in April 1983 with complaints of diminished vision associated with uniocular diplopia in the right eye of three months' duration. In the left eye she had pain and redness five months previously and had undergone lens extraction with no significant visual improvement.

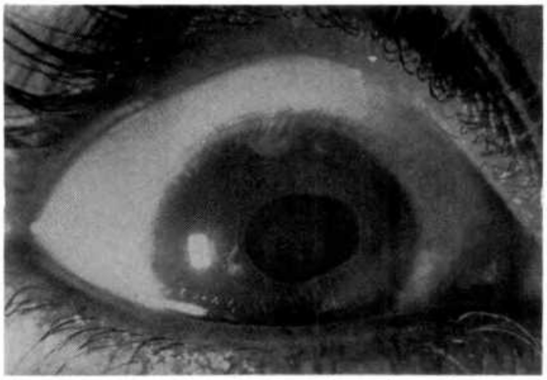

Fig. 2 *Repositioning of pupil nasally to enlarge the aphakic area.*

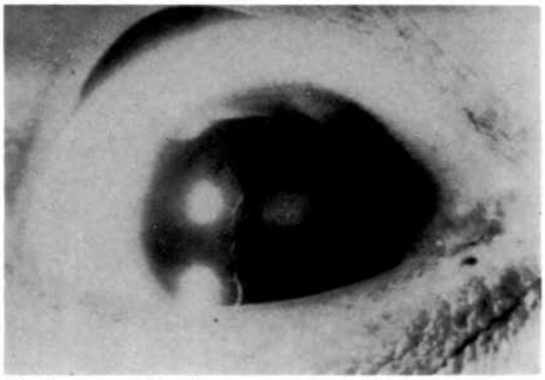

Fig. 3 *Upward displacement of pupil with iris photocoagulation.*

Physical examination revealed arachnodactyly and high arched palate. The arm span was 5 cm more than the height. However, there were no cardiovascular abnormalities. Ocular examination showed that the right eye was quiet. The anterior chamber was deep and slightly irregular with iridodonesis. The pupil was normal in size and reaction to light. The lens was partly cataractous, and visual acuity was finger counting at 1 metre. On dilatation of the pupil the lens was found to be subluxated laterally and slightly downwards, and aphakic correction afforded substantial improvement of visual acuity. In the left eye the cornea showed bullous keratopathy with pigment on posterior surface. Aphakia with herniation of vitreous into the anterior chamber was present. The IOP was 50·4 mmHg (Schiøtz tonometer) and visual acuity was finger counting at 1 metre. The best corrected visual acuity was 6/60.

In view of the disastrous postoperative course in the left eye and good visual acuity with correction of aphakic portion in the right eye, it was decided to adopt non-surgical treatment of the right eye. The aphakic area of the pupil was enlarged nasally by repositioning the pupil by iris photocoagulation. Visual acuity improved to 6/9 with +11·0 D.sph/ +1·0 D.cyl 135° (Fig. 2). The patient has been followed up for one year. She retains the same visual acuity, and the IOP is 20 mmHg.

CASE 2

A 35-year-old woman attended the Ophthalmology Outpatient Department of Jipmer Hospital in August 1983 with complaints of defective vision both eyes of two years' duration. She had undergone uneventful intracapsular lens extraction in left eye one year previously with good postoperative vision.

Examination revealed that in right eye the anterior chamber was deep and iridodonesis was present. The pupil was normal in size and reaction and the lens was cataractous, with a visual acuity of counting fingers at 0·5 metre and IOP 17·3 mmHg (Schiøtz tonometer). On dilatation of the pupil the lens was found to be displaced downwards, with good visual improvement after aphakic correction.

The left eye was aphakic, with a peripheral iridectomy. The IOP was 14·6 mmHg (Schiøtz tonometer). The visual acuity improved to 6/12 with +11·0 D.sph/ +2·0 D.cyl 165°.

In view of the subluxated lens and good visual improvement with aphakic correction a conservative approach was planned. Iris photocoagulation with xenon arc was done to pull the pupil upwards (Fig. 3). The visual acuity with +12 D.sph was 6/9.

Discussion

Lens subluxation, a displacement in which the lens remains at least partially within the pupillary area, may occur as a result of heredofamilial disorders, ocular disease, or trauma. Marfan's syndrome commonly causes it and has attracted considerable attention.[5] Glaucoma is not uncommon in eyes with lens subluxation. The clinical management of subluxated lens is based on awareness of variations in the degree of displacement and an understanding of the adverse effects of this malposition. However, therapy should always be planned to maintain and improve vision.

To accomplish this a number of measures are available. The optical correction of refractive error (phakic) due to irregular astigmatism on account of tilting of the lens is difficult and unsatisfactory; it becomes impossible in the presence of lenticular haze or opacity. Prolonged drug induced mydriasis to permit vision through the aphakic part of the pupil is possible but has the disadvantages of causing glare, drug sensitisation, and the probability of anterior dislocation of the lens. Optical iridectomy may also precipitate anterior dislocation, development of pupillary block, or even intraocular infection. Experience with these methods has revealed the limitations of optical correction, prolonged drug induced mydriasis, and the substantial hazards of intraocular surgery.[6]

This report describes an additional method of management that is highly beneficial in appropriate cases of subluxation. The method employed is iris photocoagulation to produce a permanent alteration of the pupil and permit vision through the aphakic portion of this expanded aperture (Fig. 3). The determination of the quadrant of iris to be photocoagulated in order to reposition the pupil depends on the position of the displaced lens, and it is evaluated prior to iris photocoagulation by mydriasis and refraction through the aphakic part of pupil.

The pupil can be displaced in the desired direction by iris photocoagulation, presumably owing to iris retraction, and the repositioning of the pupil can be limited to a particular segment. Since there is only localised enlargement of the pupillary aperture, the hazards associated with optical iridectomy or drug induced mydriasis are not encountered. In addition being a non-invasive procedure, the hazards of intraocular surgery are obviated. This procedure can be undertaken in the outpatient department and it is of value even for patients who are otherwise poor surgical risks[7] or who refuse surgery.

References

1 Jarret WM. Dislocation of lens. *Arch Ophthalmol* 1967; **78**: 289–93.

2 Barraquer J. Surgery of dislocated lens. *Ophthalmology (Rochester)* 1972; **76**: 44–59.

3 Straatsma BR, Allen RA, Pettit TH, Hall MO. Subluxation of lens treated with iris photocoagulation. *Am J Ophthalmol* 1966; **61**: 1312–24.

4 Peyman GA, Raichard ML, Goldberg MF, Ritacca D. Management of subluxated and dislocated lenses with the vitrophage. *Br J Ophthalmol* 1979; **63**: 771–8.

5 Francois J. *Heredity in ophthalmology*. St Louis: Mosby, 1961.

6 Chandler PA. Treatment in dislocation of lens. *Arch Ophthalmol* 1964; **71**: 765.

7 Lamba PA, Santosh KD. Repositioning of pupil for visual disability, *Indian J Leprosy* 1984; **56**: 4–9.

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Schistosomotic choroiditis.
I. Funduscopic changes and differential diagnosis

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SUMMARY This paper presents the results of biomicroscopy and funduscopy on five patients with hepatosplenic schistosomiasis mansoni. Fluorescein angioretinography was performed on two patients. All cases showed yellowish white multiple billateral nodules of various sizes, located in the choroidal plane. The nature and differential diagnosis of these nodules is discussed, and the suggestion is made that they represent cases of schistosomotic nodular choroiditis.

Schistosomiasis (*Schistosoma mansoni*, *S. haematobium*, and *S. japonicum*) is a worldwide public health problem, affecting approximately 200 million people, with roughly 10 million cases in Brazil.[1] *S. mansoni* is the most widely distributed species, present in the Caribbean Isles, South America, Africa, and Arabia, with widespread geographical extension and an increase in prevalence.[2 3]

The *S. mansoni* hepatosplenic form of the disease is both common and has serious consequences. In Brazil it affects 3 to 12% of patients with schistosomiasis.[4 5] The parasite has unusual locations in the hepatosplenic form of the disease, with 26% of the patients presenting with cerebral parasites.[6]

During funduscopic examination of a child with hepatosplenic schistosomiasis Oréfice in 1968 observed[7] yellowish white nodules of various sizes in the choroid in both eyes. This finding suggested the possibility of involvement of the uveal tract, as in cysticercosis. Further examinations of 50 patients with hepatosplenic schistosomiasis revealed four cases with similar choroidal changes.

The recent finding of schistosomotic granulomas in the choroid of a patient with hepatosplenic schisotosomiasis[8] confirms the impression that these ophthalmic changes were caused by that disease, a condition not so far described.

Case reports

CASE 1 (Neves et al., 1978)[7]

This case has been reported on by Neves *et al.*[7] It is of a girl aged 9 years, white, admitted to hospital in 1968.

Physical examination. Porta-caval type of collateral circulation. Liver palpable at 4 cm below the costal margin. Spleen palpable at 2 cm below the right costal margin and 8 cm under the xiphoid.

Laboratory tests. Stool examination showed viable

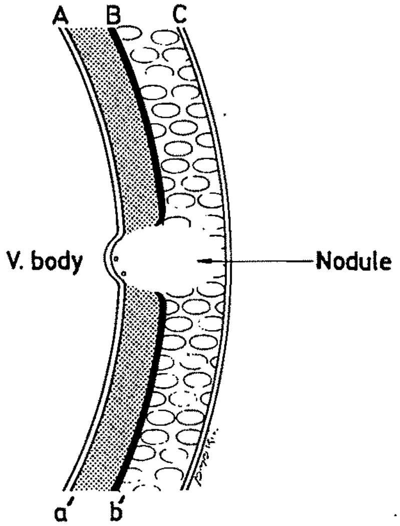

Fig. 1 *Drawing of optic section of a nodule. The anterior retina profile line* (a') *projects slightly towards the vitreous body; there is discontinuity of the posterior retina profile line* (b'). *Translucent tissue is observed in the retina and choroid.* A=*Internal limiting membrane.* B=*Pigment epithelium.* C=*Sclera.* a'=*Anterior retina profile line.* b'=*Posterior retina profile line.*

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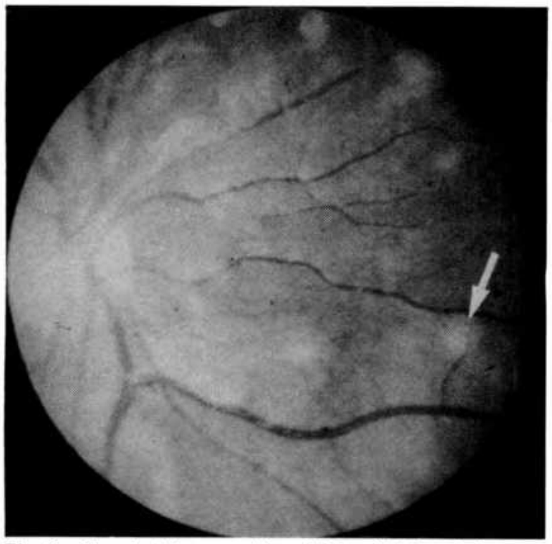

Fig. 2 *Case 1: right eye, with multiple whitish nodules, one arrowed.*

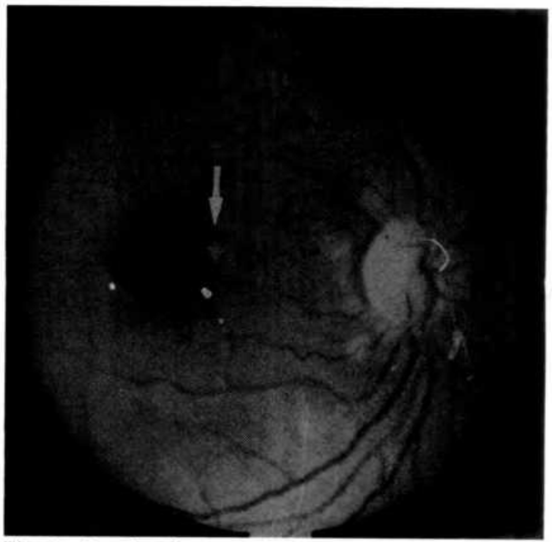

Fig. 3 *Case 2: right eye, with whitish medium sized nodules close to the optic nerve; one perifoveal nodule (arrow).*

S. mansoni ova. Mantoux test positive at 1:100 000. Chest *x* ray showed disseminated micronodules in both lungs and an increase in cardiac area. Electrocardiogram showed right ventricular overload.

Eye examination. Right eye, visual acuity 20/60 with no correction; left eye, 20/20. Intraocular pressure was 13 mmHg in both eyes. With the Goldmann-Busacca contact lens the vitreous body appeared free of inflammatory cells, even close to fundus lesions. An optic section of the nodules (Fig. 1) showed a projection of the anterior profile of the retina towards the vitreous body, and discontinuity of the posterior profile of the retina, as evidence of the lack of pigmented retinal epithelium. Indirect binocular ophthalmoscopy (Fig. 2, right eye) of both eyes disclosed the presence of numerous yellowish white translucent nodules of various sizes, distributed irregularly, but with some concentration close to the optic nerve and blood vessels. The veins were moderately engorged, and the maculae were normal.

CASE 2

A 14-year-old female, of mixed colour, was admitted to hospital in 1978.

Physical examination. Liver palpable at 12 cm below the costal margin on the hemiclavicular right line and 16 cm below the xiphoid, with a blunt edge, not painful, with a micronodular surface. Spleen palpable at 4 cm below the left costal margin on the left hemiclavicular line, with a blunt edge, not painful.

Laboratory tests. Tuberculin test was not reactive. Stool examination showed viable *S. mansoni* ova. Electrocardiogram showed right ventricular overload and diffuse ischaemia. An oesophagogram showed oesophageal varices. A chest *x* ray showed enlarged heart, mainly the right ventricle; diffuse micronodules in both lungs. Haemodynamic tests showed hypertension in right chambers and slight hypertension in left chambers. Hepatic biopsy showed granulomas suggesting schistosomotic origin. Lung biopsy showed granulomas with *S. mansoni* ova.

Eye examination. Visual acuity in both eyes was 20/20. Intraocular pressure in both eyes was 15 mmHg. Anterior chamber biomicroscopy showed no inflammatory cells. Vitreous body biomicroscopy showed rare cells. With the Goldmann-Busacca contact lens the vitreous body disclosed rare inflammatory cells and occasional nodules with a similar aspect to those in case 1. Indirect binocular ophthalmoscopy of both eyes (Figs. 3 and 4, right eye) revealed yellowish white nodules of various sizes distributed irregularly, with greater concentration around the optic nerve in the right eye. Fluorescein angioretinography of the right eye (Figs. 5 A and B, right eye) showed hyperfluorescent nodules in the posterior pole appearing in early phases, with no leakage in late phases. The left eye presented similar findings.

CASE 3

This was a man aged 35 years, of mixed colour, admitted to hospital in 1979. He had been treated for schistosomiasis with hycanthone five years before,

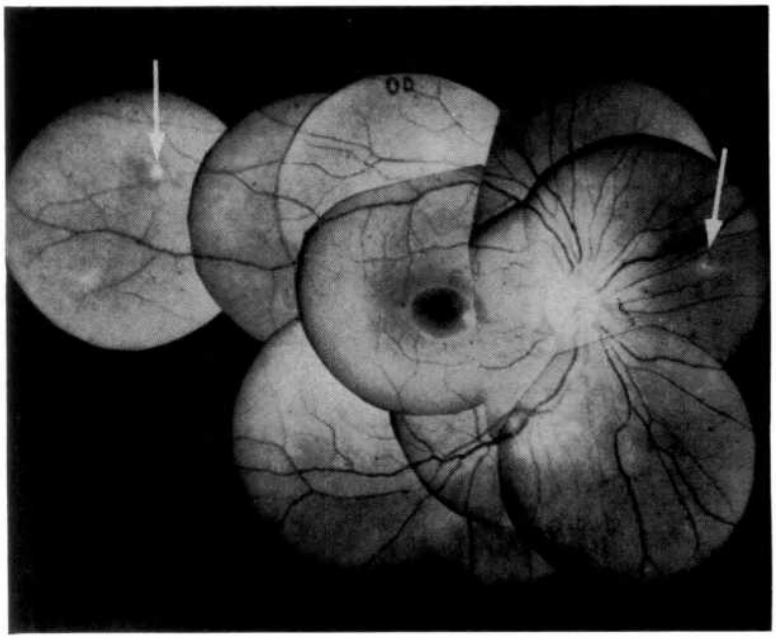

Fig. 4 *Case 2: right eye, composite fundus with green filter, showing nodule distribution (arrows).*

when he presented with portal hypertension associated with stools positive for *S. mansoni*.

Physical examination. No significant changes.

Laboratory tests. The Mantoux test was positive at 1:10 000. A brucella test was negative, and a histoplasmin test negative. A chest *x*-ray was normal. Stool examination was negative.

Eye examination. Right eye visual acuity was 20/50 with correction, left eye 20/20. The intraocular pressure was 13 mmHg in both eyes. Biomicroscopy of the anterior chamber and anterior vitreous body of both eyes revealed no inflammatory cells. Contact lens biomicroscopy was not done in this case. Indirect binocular ophthalmoscopy (Fig. 6, right eye) of both

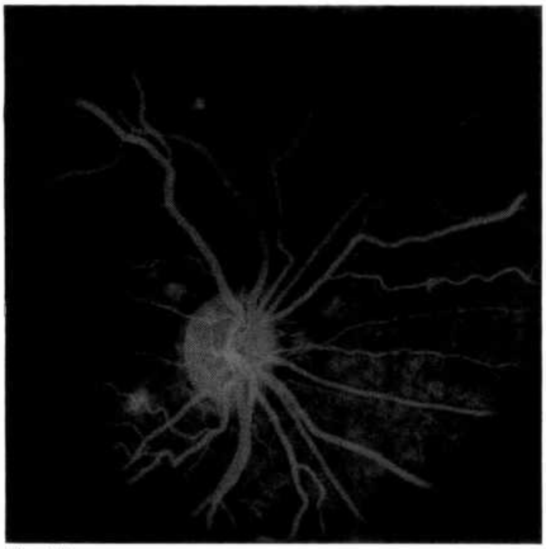

Fig. 5A

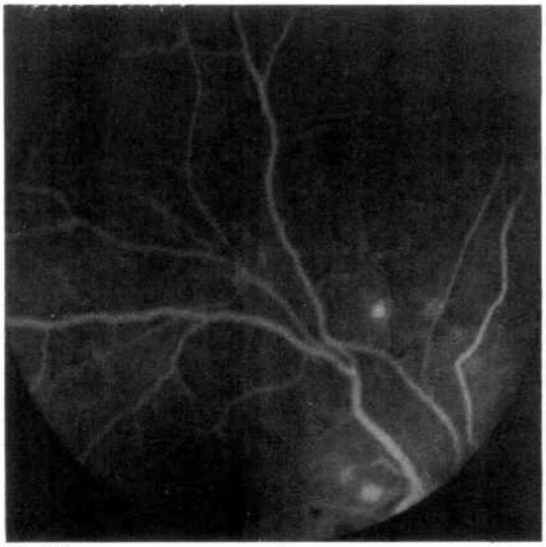

Fig. 5B

Fig. 5 *Case 2:* A: *right eye, fluorescein angioretinography (arteriovenous phase) showing hyperfluorescent nodules.* B: *nodules maintaining hyperfluorescence in later phase of the examination.*

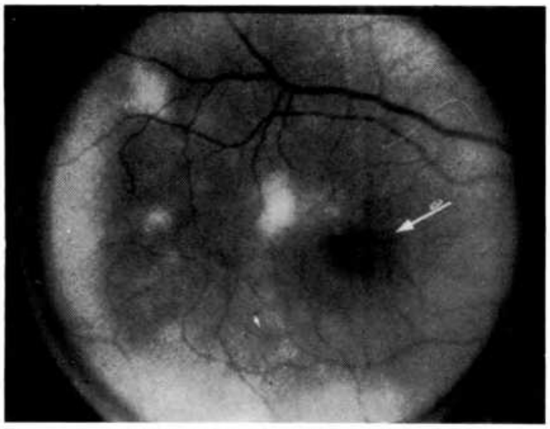

Fig. 6 *Case 3: right eye, with whitish medium sized nodules, and striation of the retinal internal limiting membrane in the macular area (arrow).*

eyes disclosed numerous yellowish white nodules with irregular distribution. The macula in the right eye presented striations on the internal limiting retinal membrane. Fluorescein angioretinography was not possible in this case.

CASE 4

This case was a 16-year-old male, of mixed colour, admitted to hospital in 1981.

Physical examination. The spleen was enlarged (Boyd type III), towards the median line, hardened, not painful. The liver was not palpable. Cardiac and lung auscultation were normal.

Laboratory tests. Stool examination was positive for *S. mansoni*. A chest *x*-ray showed signs of pulmonary hypertension and reduction in peripheral base vascularity. Upper gastrointestinal barium radiography showed oesophageal varices. Hepatic biopsy showed granuloma of possible schistosomotic origin.

Eye examination. The visual acuity for both eyes was 20/20. Intraocular pressure was 12 mmHg in both eyes. Biomicroscopy of the anterior chamber and anterior vitreous body revealed no inflammatory cells. Contact lens biomicroscopy was not done in this case. Indirect binocular ophthalmoscopy (Fig. 7, right eye) disclosed small, yellowish white translucent nodules in both eyes. The right eye showed a nodule surrounded by a haemorrhagic halo. Fluorescein angioretinography was not possible in this case.

CASE 5

This case was a 24-year-old male, white, admitted to hospital in 1982.

Physical examination. The liver was 4 cm below the costal margin, not painful.

Laboratory tests. Stool examination showed *S. mansoni* viable and non-viable ova. Oesophagogastroduodenoscopy showed medium calibre oesophageal varices. A chest *x*-ray was normal.

Eye examination. The visual acuity for both eyes was 20/20. Intraocular pressure was 16 mmHg for both eyes. Biomicroscopy of the anterior chamber and anterior vitreous body revealed no inflammatory signs. With the Goldmann-Busacca contact lens no inflammatory cells were found in the vitreous body in

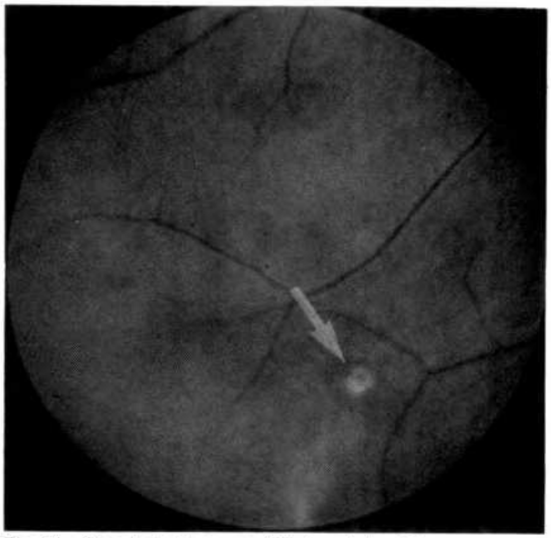

Fig. 7 *Case 4: right eye, a whitish nodule with a haemorrhagic halo (arrow).*

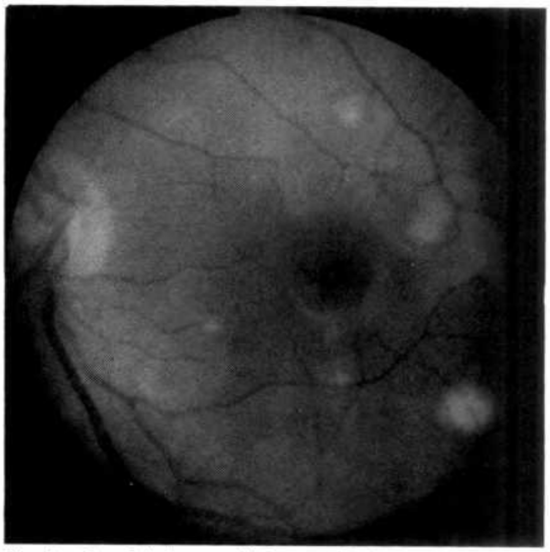

Fig. 8 *Case 5: left eye, with large, whitish, irregularly distributed nodules.*

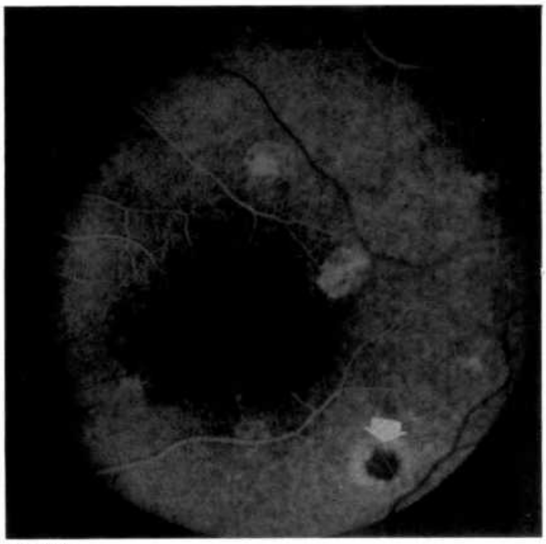

Fig. 9A

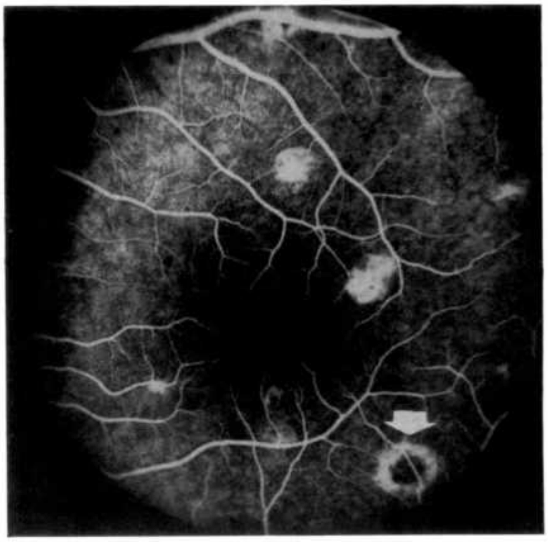

Fig. 9B

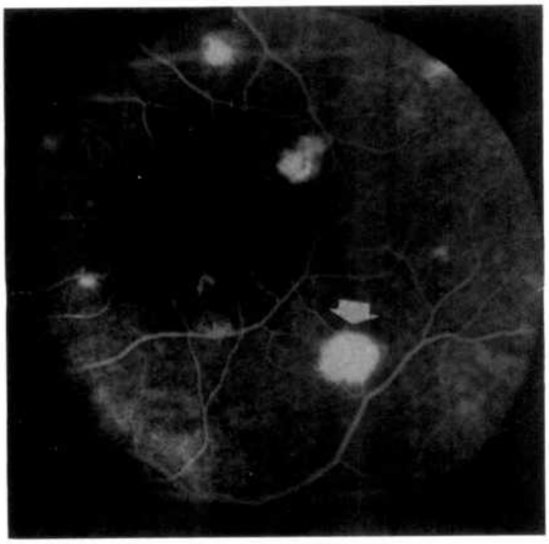

Fig. 9C

Fig. 9 *Case 5:* A: *left eye fluorescein angioretinography (arterial phase) showing hyperfluorescent nodules, and dark hypofluorescent nodule (arrow) with hyperfluorescent halo.* B: *(arterial-venous phase) maintains similar findings.* C: *(late phase) with hyperfluorescent nodule (arrow). Fluorescein angioretinography of the right eye was similar.*

either eye. A section of the eye showed nodules (Fig. 1) similar to those in case 1. Indirect binocular ophthalmoscopy disclosed yellowish white nodules of various sizes in both eyes, with irregular distribution and some concentration around the optic nerve and close to blood vessels (Fig. 8, left eye). Fluorescein angioretinography (Figs. 9A, B, C, left eye) of the left eye showed hyperfluorescent nodules in the arterial phase, and a hypofluorescent point surrounded by a hyperfluorescent halo in the lower temporal region. No change in hyperfluorescence was observed in the early arteriovenous phase. In the late phase the hypofluorescent point became hyperfluorescent. At this point the vein projected towards the vitreous body. Fluorescein angioretinography of the right eye was similar.

Discussion

These cases suggest that funduscopic changes may occur fairly frequently in hepatosplenic schistosomotic patients. Of 50 patients five were found to have such changes. These were yellowish white translucent nodules of various sizes located in the choroid, confirmed by optical section biomicroscopy and fluorescein angioretinography in three of them. In all five cases the anterior segment was not affected, and only case 2 presented a small number of cells in the vitreous body, demonstrating the choroidal location of these lesions.

It was noted that nodules did not interfere with visual acuity if the maculae was not affected. Only case 3 had macular nodules.

A comparison of these funduscopic findings with changes found in similar conditions is the aim of this paper. Our work was hampered by the lack of reported data, probably due to the fact that examination of the fundus is not routine in patients with schisotosomiasis.

Studying a group of military recruits (18–19 years of age) who had contact with river water in the vicinity of Belo Horizonte during training manoeuvers, Oréfice and Brandão (unpublished work) noted that 78 of a total of 130 recruits eliminated *S. mansoni* ova. Clinical and laboratory examinations led to the diagnosis of 39 patients in the acute phase, 17 in the chronic phase, and 22 undefined cases. All had a normal fundus on examination. No patients had the hepatosplenic form of the disease.

Few ocular findings have been attributed to *S. mansoni.*[9] Uveitis and vascular changes in the retina in patients with stools positive for *S. mansoni* have been described, suggesting a possible association.[10–15] Non-specific lesions such as retinal haemorrhage and soft and hard exudates were observed in 60 patients with hepatosplenic schistosomiasis, but we were unable to correlate these findings because other systemic changes were present.[16]

Since no histopathological examinations were possible in these cases, the fundus lesions have been analysed by the nature of the changes and the differential diagnosis from other pathological choroidal lesions. The dimension and colour of the choroidal nodules are similar to *S. mansoni* ova granulomas present in other organs of patients with schistosomiasis. We believe that the choroidal nodules are *S. mansoni* ova granuloma. The possible pathways by which *S. mansoni* eggs could reach the eye are discussed in the second part of this paper.[8]

The recent histological finding of a schistosomotic granuloma in the choroid of a patient with hepatosplenic schistosomiasis[8] confirms the hypothesis of Neves *et al.*[7] Another posibility is that these nodules are the morphological changes due to immunocomplex deposits similar to those found in renal glomeruli[17] and the choroidal plexus[18] and not an inflammatory reaction to *S. mansoni* ova. However, these mechanisms do not produce micronodular lesions visible on endoscopy.

The fundus lesions we encountered show some similarity to those that occur in chronic miliary tuberculosis. All cases were investigated for this possibility with or without positive Mantoux tests. Clinical study and follow-up allowed us to establish *S. mansoni* as responsible for the fundus lesions.

NOTE. Busacca's terminology was used in biomicroscopy.[19]

We thank Dr Renato Laender and Dr Giambatista Coscarelli for intravenous fluorescein angiography, and Mrs Claudia Lambert for drawing the optic section of the nodule.

References

1 Pessoa SB, Martins AV. Trematodeos parasitas do sistema sanguineo. *Schistosoma mansoni*—Histórico—Distribuição Geográfica—Morfologia e Biologia. In: Pessoa SB, ed. *Parasitologia Médica.* Rio de Janeiro: Guanabara Koogan, 1982: 361–81.

2 McCully RM, Barron CV, Cheever AW. Schistosomiasis. In: Benfered CH, Connor DH, eds. *Pathology of tropical and extraordinary diseases.* Washington, DC: Armed Forces Institute of Pathology, 1976: **2:** 482–3.

3 Hoffman Jr D. *Schistosomiasis research. The strategic plan.* New York: Edna McConnell Clark Foundation, 1983: 105.

4 Coutinho A, Domingues ALC. Esquistossomose mansoni. In: Dani R, Paula Castro L, Perez V, Arabehety JT, eds. *Gastroenterologia.* Rio de Janeiro: Guanabara Koogan, 1978: 850.

5 Bogliolo L. Fígado e vias biliares. In: Bogliolo L, ed. *Patologia.* 3d ed. Rio de Janeiro: Guanabara Koogan, 1981: 717.

6 Pitella JEH, Lana-Peixoto MA. Brain involvement in hepatosplenic schistosomiasis mansoni. *Brain* 1981; **104:** 621–32.

7 Neves J, Pedroso ERP, Oréfice F, *et al.* Esquistossomose pulmonar. III-Forma crônica externa com hipertensão pulmonar e na vigência de hipertensão portal associado a provável coroidite e retinite esquistossomótica. *Arq Bras Oftalmol* 1978; **41:** 215–20.

8 Pittella JEH, Oréfice F. Schistosomotic choroiditis. II. Report of first case. *Br J Ophthalmol* 1985; **69:** 300–2.

9 Cordero Moreno R. Sobre algunas lesiones oculares en la schistosomiasis mansoni. *Arch Venez Soc Oto-Rino-Laring* 1943; **2:** 158–75.

10 Cecchetto E. Il primo casi di Schistosoma mansoni riscontrato in Europa, con gravi complicazioni oculari. *Ann Ottalmol Clin Oculist* 1931; **59:** 155–8.

11 Andrade C. Esquistossomose. In: Andrade C, ed. *Oftalmologica tropical (Sul-Americana).* Rio de Janeiro: Rodrigues, Jornal do Correio—Brasil, 1940: 93–101.

12 Machado NR. Esquistossomose mansônica e oftalmologia (nota prévia). *Ophthalmol Ibero Americana* 1956; **18:** 89.

13 Queiroz JM. Aspectos experimentais e clínicos das manifestações oculares da esquistossomose mansoni. *Ophthalmol Ibero Americana* 1961; **22:** 115–226.

14 Massa MJ, Laurijs L, Wijns (Louvain). Lésions parasitaires de la retine chez une femme bantoue. *Bull Soc Belge Ophtalmol* 1964; **137:** 412–23.

15 Vedy J, Carrica A, Rivaud C, Chanut G, Graveline J. A propos d'un cas de rétinite chez un bilharzien. *Med Trop (Madr)* 1979; **39:** 603–7.

16 Lemos E. Alterações retinianas na esquistossomose hepatoesplênica. *Rev Bras Oftalmol* 1980; **39:** 123–8.

17 Hoshino-Schimizu S, Brito T, Kanamura HY, *et al.* Human schistosomiasis: *Schistosoma mansoni* antigen detection in renal glomeruli. *Trans R Soc Trop Med Hyg* 1976; **70:** 492–6.

18 Queiroz AC. Lesões da plexo coróide nas esquistossomose mansônica. *Arq Neuro-Psiquiatria (São Paulo)* 1981; **39:** 317–20.

19 Busacca A. Le fond de l'oeil. In: Busacca A, ed. *Manual de biomicroscopie oculaire.* Paris: Doin, 1966: 286–323.

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Schistosomotic choroiditis. II. Report of first case

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SUMMARY The first case of granulomatous choroiditis produced by *Schistosoma mansoni* with histological confirmation is reported. The patient had the hepatosplenic and cardiopulmonary forms of the disease and presented with cerebral schistosomiasis. The funduscopic aspects of the lesion and the possible pathways taken by the parasite to reach the choroid are discussed.

Uncommon sites for infection by *Schistosoma mansoni* seem to be associated with certain anatomicoclinical forms of the disease. One of these unusual sites, the brain, was recorded in 26% of patients with the hepatosplenic form of schistosomiasis.[1] One case has been reported of infection of the eye by an immature male *S. mansoni* parasite, in the anterior chamber.[2]

The funduscopic observation made by Oréfice *et al.*[3] of choroidal nodules in five cases of the hepatosplenic form of schistosomiasis prompted one of the authors (Pittella) to carry out a systematic search for ova and granulomas in semiserial histological sections of the eyes of two deceased patients who had the hepatosplenic form of *S. mansoni* infection. In one case *S. mansoni* ova and granulomas were found in the choroid. We report this case, as no histologically confirmed granulomatous choroidal schistosomotic infection has been reported so far.

Case report

A female aged 17 years, born in Medina (Minas Gerais State) and living in Belo Horizonte, had been asymptomatic until 1½ years ago, when she presented with dyspnoea on effort, which became worse over the next year or so. Recently she had suffered severe dyspnoea even at rest, with cough and vomiting. No palpitations or haemorrhagic sputum were noted, nor thoracic or abdominal pain.

On examination there was moderate tachydyspnoea, cyanosis, and reduced capillary perfusion, but no oedema. The blood pressure was 140/80 mmHg, the heart rate 108 per minute, with normal rhythm. The heart had a pulmonary presystolic click, with normal first and second heart sounds. There was hepatosplenomegaly. Funduscopy was not done. The patient died soon after hospital admission. The clinical diagnosis was severe pulmonary hypertension of unknown origin (cardiopulmonary schistosomiasis?).

Pathological investigations showed a schistosomotic type of Symmers hepatic fibrosis, a sclerocongestive spleen, a cardiopulmonary form of schistosomiasis, and moderate ascites. An interatrial communication was found, with patent foramen ovale, 0·4 cm diameter. Neuroschistosomiasis was present, with perivascular *S. mansoni* ova and mononuclear inflammatory infiltrate, a variable glial reaction, and occasional necrotic-exudative granulomas in the leptomeninges, cerebral cortex, and subcortical right frontal and temporal white matter, the left putamen, and close to the left dentate nucleus. Calcified *S. mansoni* ova agglomerates were present in the left lateral globus pallidus, adjacent to a small lenticulostriate artery. There were slight cerebral oedema, a small cavum septi pellucidi, and a pineal gland cyst. Anatomical variation of the circle of Willis was noted.

EYE EXAMINATION

No changes were noted macroscopically on the internal surface of the eye. Semiserial haematoxylin-eosin stained histological sections (7 μm) showed three schistosomotic granulomas characterised by embryonic and non-embryonic *S. mansoni* ova in the choroid, projecting slightly into the retina, surrounded by epithelioid cells in palisade formation and more external lymphocytes, plasmocytes, and eosinophilic granulocytes. The largest granuloma also showed periovular necrosis as a homogeneous acidophilic

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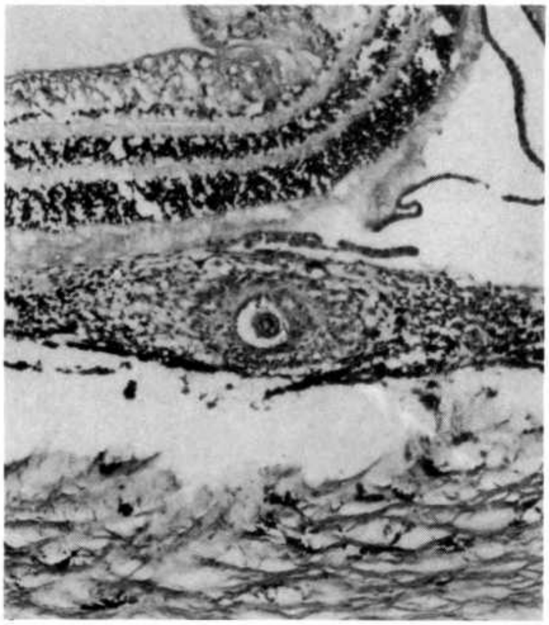


Fig. 1 *Schistosomotic granuloma in the necrotic-exudative phase in the choroid. (Haematoxylin and eosin, ×100).*

area (granuloma in the necrotic-exudative phase), which was absent in the other two granulomas—in the productive phase (Figs. 1, 2, 3).

Discussion

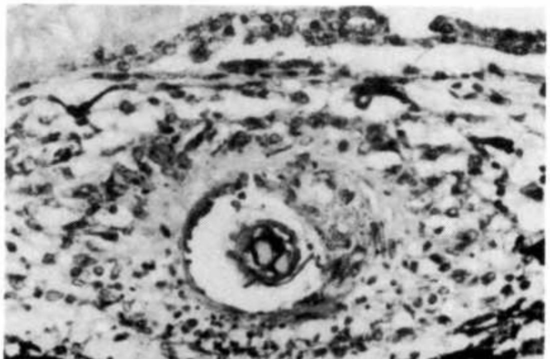


Fig. 2 *Higher magnification of Fig. 1. (Haematoxylin and eosin, ×256).*

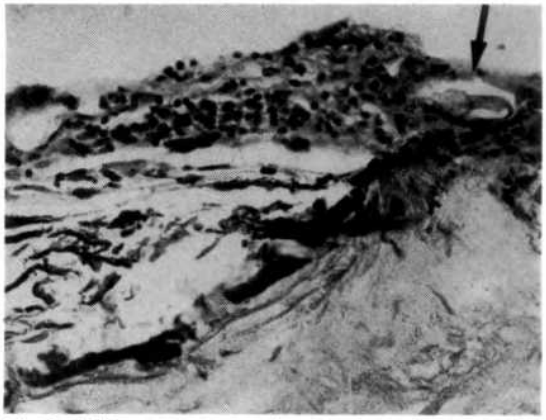


Fig. 3 *Schistosomotic granuloma in the productive phase in the choroid. Note* S. mansoni *ovum shell (arrow). Haematoxylin and eosin, ×256).*

The finding of schistosomotic granulomas in the choroid of a patient with hepatosplenic schistosomiasis mansoni confirms the suggestion made by Oréfice[4] of choroiditis caused by *S. mansoni*. These granulomas may correspond to those nodules seen at funduscopy by Oréfice *et al.*[3] One of the most important morphological characteristics of the nodules is their variation in size, which may be correlated with different phases in their development, as was noted in our case. As in the present case the patients studied by Oréfice *et al.*[3] presented with hepatosplenic schistosomiasis and, with one exception, the cardiopulmonary form. Another point to be mentioned is the finding of *S. mansoni* ova in the brain. Cerebral parasitism in schistosomiasis mansoni is found in 26% of patients with the hepatosplenic form[1]; most of these cases also presented with the cardiopulmonary form of the disease.

The possible pathways by which ova might arrive at the choroid are worth considering. The discussion in Pittella and Lana-Peixoto[1] on cerebral schistosomiasis is pertinent. There are two possibilities: embolism of ova through the arterial or retrograde venous systems, and local laying of ova following anomalous parasite migration. Arterial embolism requires the presence of pre-existing pulmonary arteriovenous shunts[5,6] or shunts related to the parasitism.[7,8] However, vascular changes in pulmonary schistosomiasis which were interpreted as arteriovenous fistulae are at present considered to result from the organisation of thrombi in the pulmonary arterial circulation.[6] Two alternative routes for arterial ova embolism to the choroid are the porto-pulmonary azygous anastomosis,[9,10] favoured by the portal hypertension in our reported case, or the passage of ova to the systemic circulation through direct communication between the right and left heart, which was found in our case.

On the other hand ova might arrive at the choroid by retrograde venous routes through anastomosis between the ophthalmic vein, the cavernous sinus, cerebral veins, the spinal cord, and the portal system by means of the vertebral venous plexus of Batson.[11]

The increase in flow due to portal hypertension would favour the spreading of ova by this route.[12]

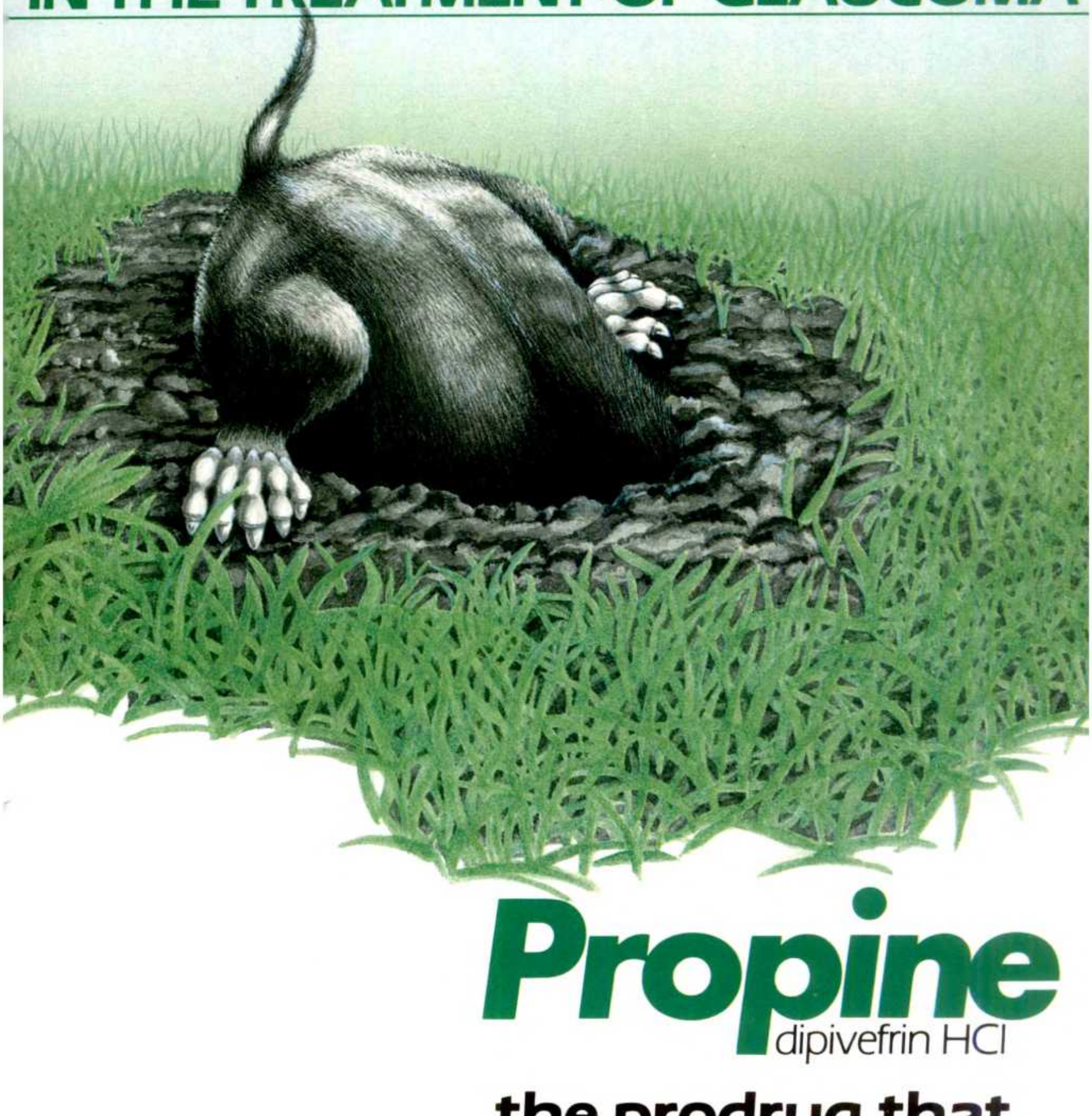
Ova lying in the choroid following anomalous parasite migration in the venous circulation can be postulated after the finding of a pair of ova of *S. haematobium* in the orbital vein of a 12-year-old child[13] and ova agglomerates at a similar site in cases of conjunctival and lacrimal gland bilharzia.[13-15] In our case an agglomerate of ova was found in the globus pallidus, a finding already noted in other parts of the brain and spinal cord in cases of schistosomiasis mansoni,[16-18] haematobium,[19 20] and japonica.[21-23] Similarly, adult parasites have been found in the central nervous system in a few cases.[7 20 24] Finally, another possibility by which ocular *S. mansoni* infection may occur is the entry of cercariae through the conjunctiva and a posterior local parasite maturing.[2 13 25] However, in experimental models Queiroz,[26] Abboud *et al.*,[27] and Lester and Freeman[28] showed that ocular entry of the parasite is not responsible for unusual eye lesions, resulting only in hepatointestinal schistosomiasis.

The authors thank Dr C J Simal for reviewing part of the literature consulted in this paper.

References

1. Pittella JEH, Lana-Peixoto MA. Brain involvement in hepatosplenic schistosomiasis mansoni. *Brain* 1981; **104:** 621–32.
2. Newton JC, Kanchanaranya C, Previte LR Jr. Intraocular *Schistosoma mansoni*. *Am J Ophthalmol* 1968; **65:** 774–8.
3. Oréfice F, Simal CJ, Pittella JEH. Schistosomotic choroiditis. I. Funduscopic changes and differential diagnosis. *Br J Ophthalmol* 1985; **69:** 294-9.
4. Neves J, Pedroso ERP, Oréfice F, *et al.* Esquistossomose pulmonar. III. Forma crônica extensa com hipertensão pulmonar e na vigência de hipertensão portal associado a provável coroidite e retinite esquistossomótica. *Arq Bras Oftalmol* 1978; **41:** 215–20.
5. Hayek H von. *Die menschliche Lunge.* 2nd ed. Berlin: Springer, 1970: 302-6.
6. Spencer H. *Pathology of the lung.* 3rd ed. Oxford: Pergamon Press, 1977: chapters 2, 10, and 16.
7. Barros OM, Giannoni FG, Marigo C, Frizzo FJ. Cor pulmonale e miocardite esquistossomóticos. Considerações clínico-pathológicas a propósito de dois casos. *Arq Hosp Santa Casa S Paulo* 1956; **2:** 33–72.
8. Faria JL. Pulmonary arteriovenous fistulas and arterial distribution of eggs of *Schistosoma mansoni*. *Am J Trop Med Hyg* 1956; **5:** 860–2.
9. Calabresi P, Abelmann WH. Portocaval and portopulmonary anastomoses in Laennec's cirrhosis and in heart failure. *J CLin Invest* 1957; **36:** 1257–65.
10. Stein H, Stein S. Digital clubbing in cirrhosis of the liver. *Lancet* 1961; **ii:** 999–1000.
11. Batson OV. The function of the vertebral veins and their role in the spread of metastasis. *Ann Surg* 1940; **112:** 138–49.
12. Faust EC. An inquiry into the ectopic lesions in schistosomiasis. *Am J Trop Med Hyg* 1948; **28:** 175–9.
13. Badir G. Schistosomiasis of the conjunctiva. *Br J Ophthalmol* 1946; **30:** 215–21.
14. Welsh NH. Bilharzial conjunctivitis. *Am J Ophthalmol* 1968; **66:** 933–8.
15. Jakobiec FA, Gess L, Zimmerman LE. Granulomatous dacryoadenitis caused by *Schistosoma haematobium*. *Arch Ophthalmol* 1977; **95:** 278–80.
16. Espin J. Mielitis producida por huevos de *Schistosoma mansoni*. *Rev Policl Caracas* 1941; **10:** 245–59.
17. Alemán GC. Localizacion ectopica aparentemente asintomatica de huevos de *Schistosoma mansoni* en el encefalo. Reporte de cuatro casos. *Arch Hosp Vargas* 1966; **8:** 71–84.
18. Budzilovich GN, Most H, Feigin I. Pathogenesis and latency of spinal cord schistosomiasis. *Arch Pathol* 1964; **77:** 383–8.
19. Gelfand M. *Schistosomiasis in South Central Africa.* Cape Town and Johannesburg: Juta, 1950: 194–202.
20. Chitiyo ME. Schistosomal involvement of the choroid plexus. *Centr Afr J Med* 1972; **18:** 45–7.
21. Greenfield JG, Pritchard B. Cerebral infection with *Schistosomiasis japonica*. *Brain* 1937; **60:** 361–72.
22. Chang TH, Smith GW, Riesenman FR, Alston EF. Cerebral granuloma due to schistosomiasis. *JAMA* 1948; **136:** 230–8.
23. Torres ML Jr. Cerebral schistosomiasis: clinical report of a proven cerebral granuloma and review of 41 other proven cases in the literature. *Philipp J Surg Surgical Specialities* 1965; **20:** 289–307.
24. Raper AB. Cerebral schistosomiasis. *East Afr Med J* 1948; **25:** 262–3.
25. Diamantis A. Les tactismes en bilharziose. *C R Congr Int Med Trop Hyg* (Cairo, 1928) 1932; **4:** 797–816.
26. Queiroz JM de. Aspectos experimentais e clínicos das manifestações oculares da esquistossomose mansoni. *Ophthalmol Ibero Americana* 1961; **22:** 115–78.
27. Abboud IA, Hanna LS, Ragab HAA. Experimental ocular schistosomiasis. *Br J Ophthalmol* 1971; **55:** 106–15.
28. Lester RJG, Freeman RS. Eye penetration by cercariae of *Schistosoma mansoni*. *J Parasitol* 1975; **61:** 970–2.

ANNOUNCING A FIRST IN THE TREATMENT OF GLAUCOMA



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White thrombi in massive subchoroidal haemorrhage: indicators of the site of its origin and of the mechanism of its control

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SUMMARY Sharply circumscribed white thrombi with well developed Zahn's lines resembling the free-floating ball thrombi occurring in the auricles of the heart are demonstrated histologically at the end of ruptured ciliary arteries, causing massive subchoroidal haemorrhages in two degenerated human eyes. Not only do white thrombi in subchoroidal haemorrhages, in principle, serve as indicators for the exact location of the bleeding vessel, but their formation also allows for an understanding of the natural control of arterial bleeding in the eye.

Clearly demarcated white thrombi with Zahn's lines are a new and significant observation in eyes with massive subchoroidal haemorrhages. However, white thrombi are very well known to general pathologists.[1 2] The principles of white thrombus formation are simple: when flowing blood leaves the lumen of blood vessels covered by endothelium or makes contact with areas of endothelial damage within blood vessels, blood platelets become activated. They cause local precipitation of fibrin from the blood serum. The resulting coagulum sticks to the exposed tissues or to the area of damaged endothelium. Erythrocytes are not usually involved. This is how small blood vessels are patched until the endothelium under the coagulum can regenerate.

In larger endothelial defects or vascular rupture the coagulum of blood platelets and fibrin sticks to the margin of exposed tissues and grows by the coalescence of more platelets and fibrin, until a so-called white thrombus is formed. In the end this will be massive and stop even the fast blood flow originating from an arterial rupture. When the formation of white thrombi takes place in flowing blood, linear markings known as Zahn's lines[1] typically develop. These indicate progressive growth of white thrombi without primary involvement of erythrocytes. Like sandbanks in winding rivers, Zahn's lines in white thrombi form in zones of locally slowing blood flow.[2] Histologically these lines are seen as coralloid or concentric linear patterns.

To give a histopathological demonstration of well developed white thrombi at the distal end of ruptured ciliary arteries causing massive bleeding in the subchoroidal space is the purpose of the present paper.

Case reports

CASE 1

This 45-year-old white male had a 10-year history of absolute glaucoma resulting from traumatic corneal perforation in his right eye. In addition to being totally blind the eye had become unsightly because of corneal scarring and neovascularisation. In January 1984 the patient developed severe pain and irritation in this eye. Examination by his local ophthalmologist revealed rupture of a staphyloma temporal to the limbus associated with a total hyphaema. Enucleation was recommended and performed by this ophthalmologist on 9 January 1984. In the process of enucleating the soft eye with its anterior rupture, another hole was made in the posterior sclera, when the optic nerve was cut in the plane of the optic nerve head. But the ocular contents remained intact and were completely removed. The eye was placed in 10% formalin for fixation and sent for pathological examination.

At gross examination the eye measured 28×21×20 mm. The cornea was diffusely scarred but was of normal size. A staphyloma in the region of the ciliary

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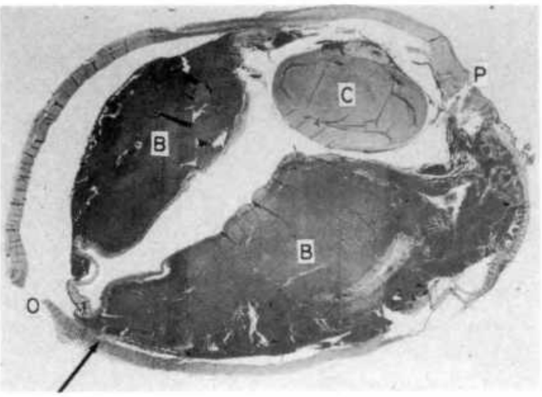

Fig. 1 *Case 1. Cross-section of eye in horizontal plane showing perforated staphyloma* (P), *cataract* (C), *massive blood* (B) *in the subchoroidal space, and scleral hole in the place of the optic nerve* (O). *Arrow indicates area of the arterial rupture. (Paraffin section, H and E stain, ×3).*

body on the temporal side was ruptured. Another round hole was found in the sclera near the optic nerve, but the structures of the optic nerve head with the surrounding uvea were preserved in their continuity. The vitreous space had not been opened. No uveal tissues were exposed in the region of this posterior hole. When the eye was opened in a horizontal plane, the anterior chamber was found to be very shallow, and the lens was large and cataractous. The choroid and retina were totally detached as a unit. A massive haemorrhage filled the subchoroidal space.

Histological study of sections cut in the horizontal plane revealed pannus formation and general degeneration in the cornea. The filtration angle was obstructed by peripheral anterior synechiae. The lens was cataractous and showed fibrous metaplasia of anterior lens epithelium as well as degeneration and calcification of lens fibres. The clinically and grossly observed rupture of the staphyloma on the temporal aspect of the anterior sclera was histologically confirmed (Fig. 1), and there was advanced atrophy of the ciliary body in the region of the staphyloma. The retina showed mainly the type of atrophy of its innermost layers that is typical of advanced glaucoma. Retina, pigment epithelium, and choroid were detached as a unit (Fig. 1). A massive haemorrhage composed of very well preserved erythrocytes filled the subchoroidal space (Fig. 1). The sclera was thinned and perforated in the region of the staphyloma. It had an additional hole posteriorly, where the optic nerve had been cut off during the enucleation (Figs. 1 and 2). The continuity of retina and optic disc was preserved in the region of the posterior scleral hole.

The stumps of two adjacent and relatively large branches of a posterior ciliary artery, ruptured next to their exit from the scleral canal into the plane of the posterior choroid, were found on the outer aspect of the pooled subchoroidal haemorrhage—widely separated by this from the further course of these arterial branches in the detached choroid (Figs. 2–4). The sharply outlined formation of a typical white thrombus with distinctly visible lines of Zahn was seen at the inner aspect of the two arterial stumps (Figs. 2–4). This white clot was a double formation joined into one as result of the close proximity of the two

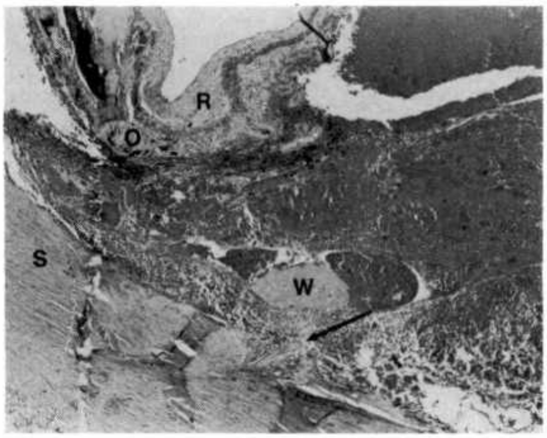

Fig. 2 *Case 1. Low-power view of the white clot* (W) *surrounded by massive subchoroidal haemorrhage with detached choroid and retina* (R) *above and sclera* (S) *below. Portions of optic disc* (O) *are seen and arrow points to ruptured ciliary arteries. (Paraffin section, H and E stain, ×40).*

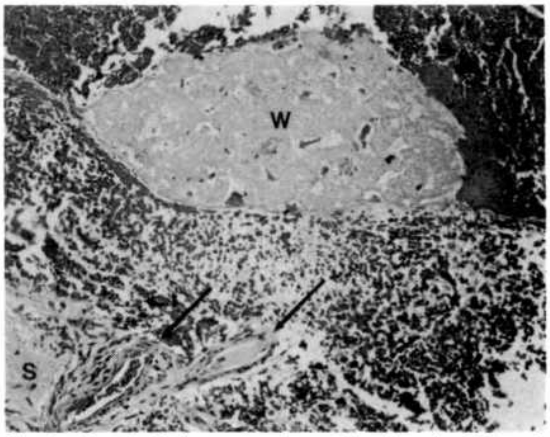

Fig. 3 *Case 1. Higher power view of the white clot* (W) *and the two ruptured ciliary arteries* (arrows) *seen in Fig. 2. A portion of sclera* (S) *on lower left. (Paraffin section, H and E stain, ×150).*

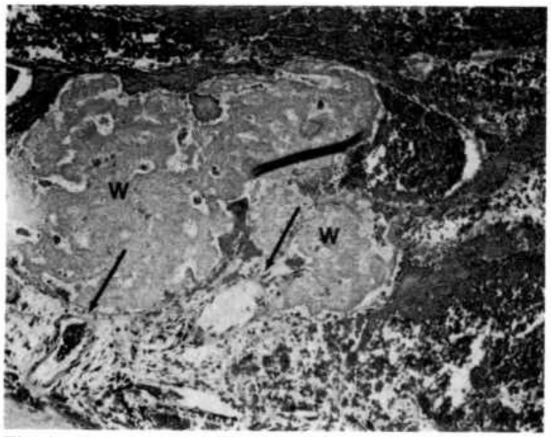

Fig. 4 *Case 1. Joined double white clots* (W, W) *above two ruptured ciliary arteries* (arrows) *in the pool of subchoroidal blood. Small portion of sclera seen in left lower corner. (Paraffin section, H and E stain, ×300).*

leaking arteries (Fig. 4). The white clot was surrounded by the pool of relatively fresh blood of the massive subchoroidal haemorrhage. The lumen of the arterial stumps was filled by a mixture of exudate-like plasma and some blood indicating absence of blood flow in these arteries at the time of the enucleation (Fig. 4).

CASE 2

This 34-year-old male with juvenile-onset type of diabetes mellitus had a history of proliferative diabetic retinopathy and repeated vitreous haemorrhages in his left eye. The eye was treated with photocoagulations in 1981 and 1982. Vitrectomy and extraction of a secondary cataract were done in 1983. Retinal detachment developed later in 1983, and an operation for it was unsuccessful. The eye had become completely blind by December 1983. Several episodes of extensive intraocular bleeding were observed. Rubeosis and blood staining of the cornea developed. The eye became hypotonic, and this was explained by detachment of the ciliary body associated with the pull of a shrinking scar of organised vitreous. Additional bleeding finally caused a rise of intraocular pressure and much pain early in 1984. The blind and painful left eye was enucleated on 23 February 1984, fixed in formalin, and sent for pathological examination.

The eyeball measured 23×19×19 mm. The cornea was involved with blood staining and scarring, but it was not shrunken. The anterior chamber was deep and filled with blood. Iris and totally detached retina were involved with massive scarring in the centre of the eye. Blood filled the subretinal and subchoroidal spaces. The blood in the subchoroidal space appeared to be fresh and most of it ran out when the eye was opened. The sclera was thickened diffusely.

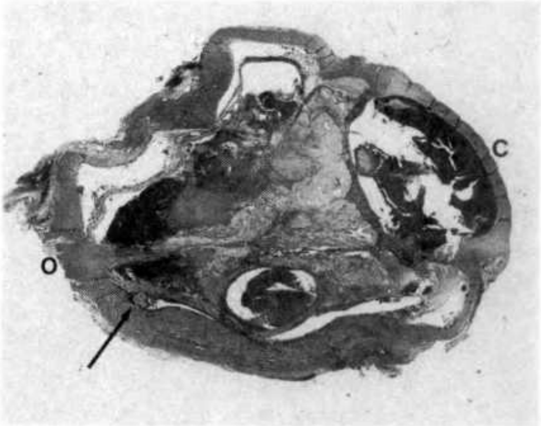

Fig. 5 *Case 2. Cross-section of eye in horizontal plane with cornea* (C), *blood in anterior chamber, aphakia, total retinal detachment, subretinal haemorrhage in different stages, choroidal detachment, and subchoroidal haemorrhage containing a white clot* (arrow). *Optic nerve* (O). *(Paraffin section, H and E stain, ×3).*

Paraffin sections cut in a horizontal plane confirmed the presence of neovascularisation, blood staining, and diffuse scarring in the cornea. The angle was open, and the trabecular meshwork contained macrophages filled with blood remnants. The iris was involved with rubeosis on its front surface, and its back was fixed to firm scar tissue containing lens remnants. This was tightly connected to the totally detached retina and formed a firm mass in the centre of the eye (Fig. 5). The retroretinal space was filled with a mixture of fresh and partly organised old haemorrhage. Ciliary body and choroid were also totally detached and had remnants of fresh blood in the subchoroidal space (Fig. 5). The sclera showed the diffuse thickening typical for phthisis.

The stump of a ruptured posterior ciliary artery was found surrounded by a pool of fresh subchoroidal haemorrhage near its inner scleral exit in the region of the posterior pole (Figs. 5, 6). A very well developed white clot with clear outer limits and distinct Zahn's lines had formed within this subchoroidal haemorrhage at the end of the arterial stump. The arterial lumen was histologically seen to be open towards the clot. The lumen of the artery contained exudate mixed with blood (Fig. 6). In this case another adjacent ciliary artery on its way into the choroid had remained continuous. Most choroidal arteries and retinal arterioles in this eye had advanced arteriolosclerotic changes, but the ruptured ciliary artery did not show obvious signs of severe involvement of this kind (Fig. 6).

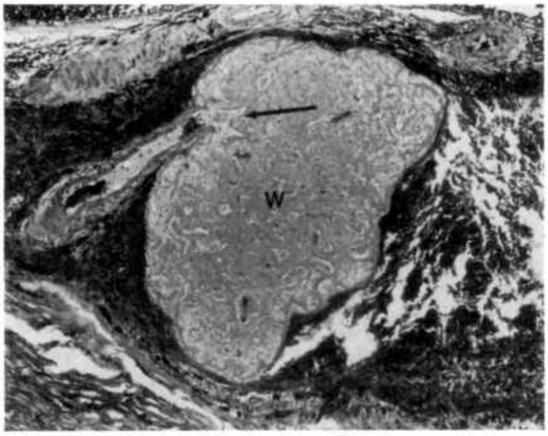

Fig. 6 *Case 2. The white clot* (W) *of Fig. 5 seen at higher power, surrounded by subchoroidal haemorrhage above open lumen* (arrow) *of separated ciliary artery. A continuous ciliary artery seen above white clot. Portion of sclera below. (Paraffin section, H and E stain, ×150).*

Discussion

Sudden hypotony is the commonest cause of massive arterial haemorrhage into the potential subchoroidal space of the eye. This type of bleeding is known as expulsive haemorrhage[3] when it occurs during surgery, but it is very similar in cases with sudden hypotony due to other causes. Intraocular arteries are not built to withstand variations in blood pressure without the support of the intraocular pressure. They have a tendency to burst when the supporting intraocular pressure is lost. In a study of the eye of a 71-year-old man with expulsive haemorrhage complicating a cataract operation rupture of the long posterior ciliary artery on the nasal side at its scleral exit was recognised as the cause of the massive subchoroidal bleeding. Granulation tissue containing new-formed primitive blood channels had formed at the distal end of the artery three weeks following the rupture in that case.[3]

The white thrombi at the distal end of ruptured ciliary arteries in the present cases were important to the eye pathologist for the localisation of the arterial bleeding. It is much easier to find the relatively large white thrombi in serial sections than it is to detect the ruptured arteries. The double arterial ruptures in the first case reported here indicate that massive arterial haemorrhage into the subchoroidal space can be due to more than one ruptured ciliary artery.

As elsewhere, white thrombi in massive haemorrhages of the inner eye are understood as nature's first repair of bleeding arteries. The mechanism of this repair should be well understood by the surgeon. For this mechanism to function the patient needs a good supply of blood platelets. To slow the arterial bleeding mechanically, when this has occurred during surgery, also makes sense. This is done by the time-honoured temporary tying of corneal sutures and additional application of finger pressure to the eye. Early drainage of a massive subchoroidal haemorrhage by sclerotomy, in contrast, would probably not help with the formation of a white thrombus. An early sclerotomy gives an outflow to the otherwise stagnant pool of blood in the subchoroidal space and could thus decrease the chances of the quickest possible thrombus formation. A sclerotomy can be done after the thrombus has formed and has caused the bleeding to stop.[4-6]

White thrombi occurring at the site of vascular rupture in the eye, in general, are not only a stage of vascular repair, for the substance of these thrombi also serves as the matrix that supports the new vascular channels which form in place of the interrupted ones. Basic knowledge about white thrombi will thus be helpful for an understanding and for clinical guidance on revascularisation as well as neovascularisation in all ocular tissues, including the retina.

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References

1 Ober WB, Friedrich Wilhelm Zahn 1845–1904: What's my line? *Pathology annual 1978*. New York: Appleton, Century, Crofts, 1978: 165–73.

2 Walter JB, Israel MS. *General pathology*. 2nd ed. Boston: Little, Brown, 1965: 733.

3 Wolter JR. Expulsive hemorrhage, a study of histopathological details. *Albrecht von Graefes Arch Klin Ophthalmol* 1982; **219:** 155–8.

4 Verhoeff FH. Sceral puncture of expulsive subchoroidal hemorrhage following sclerotomy. *Ophthalmic Rec* 1915; **24:** 55–99.

5 Vail D. Posterior sclerotomy as a form of treatment in subchoroidal expulsive hemorrhage. *Am J Ophthalmol* 1938; **21:** 256–60.

6 Wolter JR. Expulsive hemorrhage during retinal detachment surgery: a case with survival of the eye after Verhoeff sclerotomy. *Am J Ophthalmol* 1961; **51:** 264–6.

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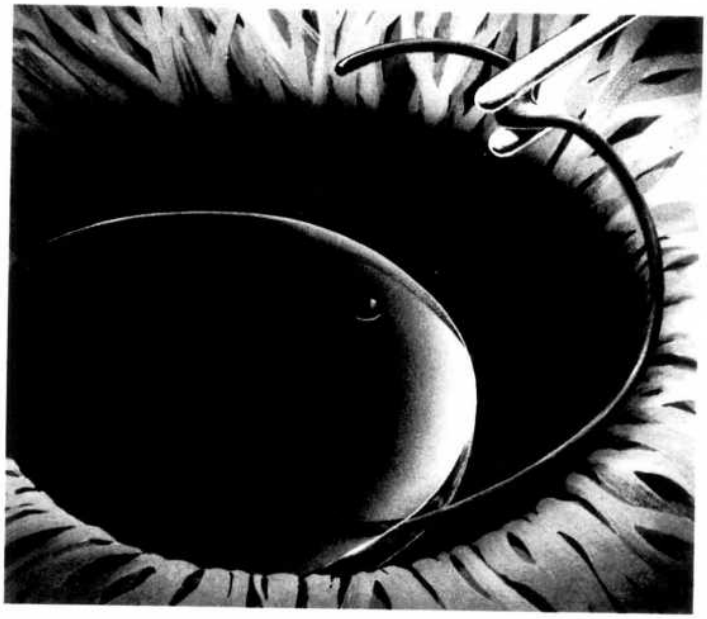

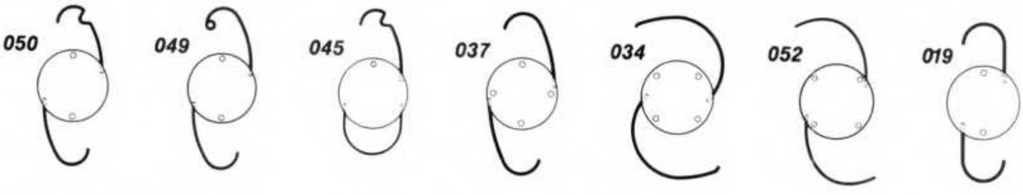

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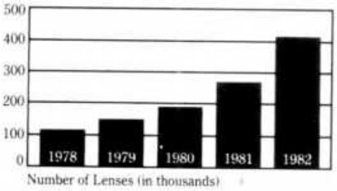

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Case of true cyclopia

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SUMMARY True cyclopia is a rare anomaly in which the organogenetic development of the two separate eyes is suppressed. A case of true cyclopia with normal karyotype is presented. There was a history of the use of an intrauterine device for contraception and of drug ingestion during early pregnancy. An anatomicopathological study of the monster with detailed presentation of the cyclopean eye is reported. The possible causes of cyclopia with particular relation to this case are discussed.

Cyclopia is an unusual anomaly in which the anterior brain and the midline mesodermal structures develop anomalously. The orbital region is grossly deformed, resulting in the formation of a central cavity 'pseudo-orbit,' with absence of nasal cavity and presence of a rudimentary proboscis above the pseudo-orbit. If two globes are found in a different degree of fusion in the pseudo-orbit, the condition is called synophthalmos. A much rarer anomaly is true cyclopia, wherein only one eye is present.[1 2]

Exposure to drugs or to other potentially teratogenic environmental factors during organogenesis has been regarded as the basis of this anomaly. These factors were ionic radiation, contraceptives, viraemia plus corticosteroids and salicylates, rubella vaccine, antibiotics, and amidopyrine (aminopyrine).[3 4]

Genetic errors with chromosomal abnormalities such as trisomy-D, monosomy-G mosaicism, translocation affecting chromosome 3 and group C chromosome, and chromosome 10 short arm deletion have also been recorded in cyclopia.[1 5–13]

In most of the recent reports there was no detailed description of the histopathological findings of the eyeball with reference to the presence of true cyclopia or synophthalmos.[3–13] We give here a detailed presentation of a case of true cyclopia where complete fusion of the two eyes was found, together with a detailed description of the histopathological findings in the pseudo-orbit, with particular reference to the history of the pregnancy, drug ingestion, and possible environmental factors during pregnancy.

Case report

The cyclop was a female infant weighing 2820 g born on the 13 August 1982 at 33 weeks gestation with vertex presentation; she lived for about 30 minutes (Fig. 1). The birth was the product of the ninth pregnancy of a 34-year-old Arab woman, para 9, married to her first cousin on her father's side. All her previous pregnancies and deliveries were normal. Her sixth delivery was twins.

About four years before her last pregnancy she was injected twice, at six-month intervals, with medroxyprogesterone acetate for birth control, after which she had her eighth pregnancy and delivery without any complications. Her last menstrual period before the last pregnancy, was on 23 December 1981. On 31 December 1981 an intrauterine device made of polyethylene and copper was inserted, and a course of tranexamic acid (Hexacaprone) one tablet three times daily for five days and ampicillin 500 mg four times daily were given for two weeks to prevent haemorrhage and infection after introduction of the intrauterine device. The pregnancy progressed with polyhydramnios, and three weeks before birth the mother was exposed to *x* rays for the diagnosis of swelling and tenderness in her right calf.

On 13 August 1982 a female cyclopean monster was born spontaneously with cephalic (vertex) presentation. She moved her hands and legs moderately and had a corneal reflex, as was reported by the obstetrician. She died about 30 minutes after birth from respiratory distress. The placenta was expelled 20 minutes later and weighed 650 g. There were three blood vessels in the cord.

Chromosomal studies of blood cell cultures from the cord and the peripheral blood taken from the parents showed a normal karyotype.

NECROPSY

On post-mortem examination malformations were

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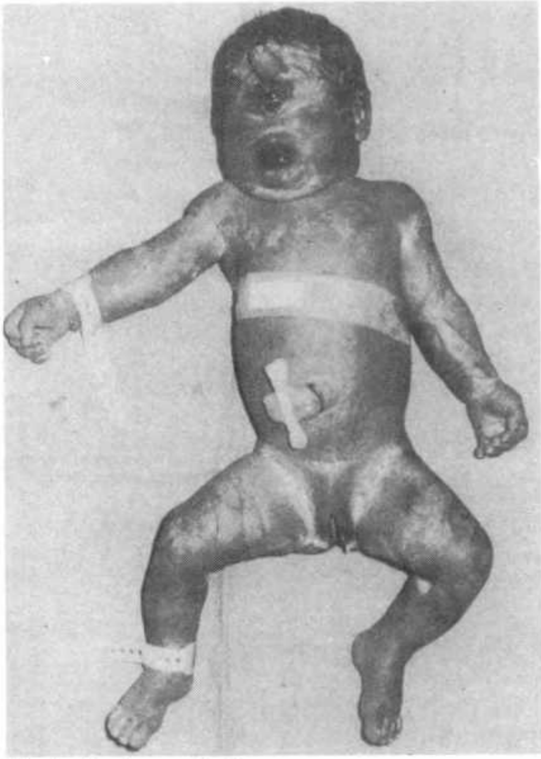

Fig. 1 *Newborn cyclopian monster.*

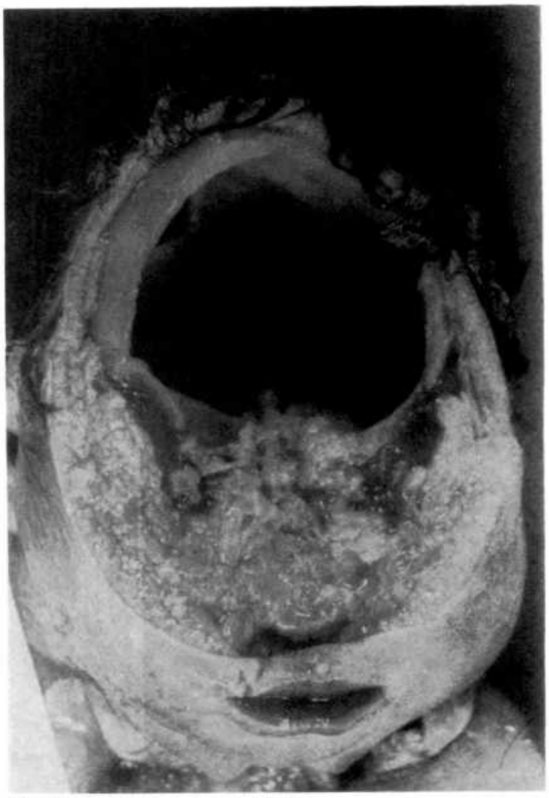

Fig. 2 *Large dorsal cyst of brain.*

discovered mainly in the face and the central nervous system. In the other systems the only defect was a patent ductus arteriosus. The outer appearance of the body and limbs was normal; anatomicopathological study of the other organ systems, including respiratory, digestive, urogenital, and endocrine, showed normal organs.

The head was well shaped. In the face (Fig. 1) there was a single median diamond shaped orbit with a single well developed globe covered by two pairs of eyelids which were developed laterally and joined into the midline by a notch or indentation. There were four lacrimal puncta. A proboscis measuring 25 mm in length and 10 mm in diameter with a single blind end orifice was attached to the superior aspect of the orbit. There were no abnormalities of the palate, pharynx, and larynx. The nose was absent.

Examination of the central nervous system revealed an 80 g brain (third of the normal weight for its age) covered by a large dorsal cyst (Fig. 2). The cerebrum was not divided into hemispheres and the sulci and gyri were not as prominent or as clearly marked as in the case of a normal brain at term. There was no olfactory apparatus, no optic chiasma, and no optic tracts or pituitary gland. Only one median connection was seen between a single optic foramen and the eyeball, which was presumed to be the sheaths of the optic nerve. On coronal section of the brain no midline dividing structures such as corpus callosum and septum pellucidum were found, and the common ventricle of the telencephalon was not divided into distinct lateral ventricles, but formed a large horseshoe shaped space which opened posteriorly into the large dorsal cyst.

The pseudo-orbit presented the appearance of fusion of the temporal halves of two orbits. Radiographic findings showed hypoplasia of frontal, ethmoidal, sphenoid, maxillary, and zygomatic bones and absence of nasal, vomerine, and lacrimal bones. A single optic nerve canal was present in the apex of the pseudo-orbit in the midline portion of the sphenoidal bone.

The orbit contained one well developed cyclopian eye (Fig. 3), striated muscles, hypertrophic nerves with increased number of Schwann cells, fat tissue, and connective tissue. On serial sections of the connection supposed to be optic nerve no nerve fibres were found.

Histopathological examination of the eyeball revealed a sclera of normal thickness (Fig. 4), a

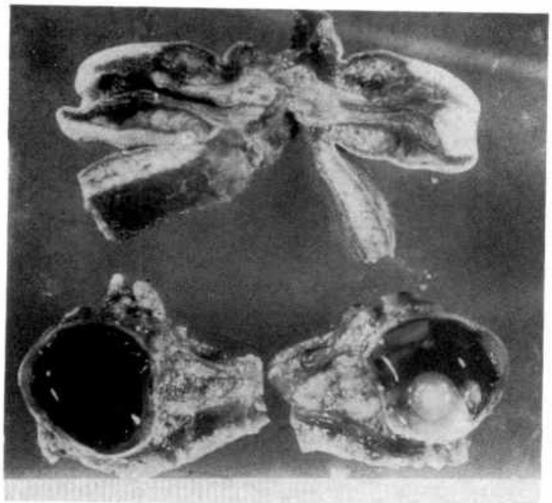

Fig. 3 *Macroscopic section of the proboscis* (above) *and of the cyclopic eyeball* (below).

hypercellular cornea, congested iris with sphincter muscle, but no dilator muscle or endothelial cells on its anterior surface were found (Fig. 5). The ciliary body presented anterior insertion of the ciliary processes, which were also short (Figs. 4, 5). The pars plana was very short, and the transformation of the ciliary pigment epithelium into retinal pigment epithelium was sudden in some places (Fig. 5). The choroid was congested, and there were some areas where it could not be recognised. The retina was disorganised and incompletely developed with areas of retinal dysplasia and formation of rosettes. Only here and there were glial cells found. There were no ganglion cells or nerve fibres. In the periphery ciliary epithelium changed abruptly into retina and then changed into a primitive neuroectoderm resembling non-pigmented epithelium. Retinal tissue projected into the vitreous (Fig. 6) and in some areas into the sclera.

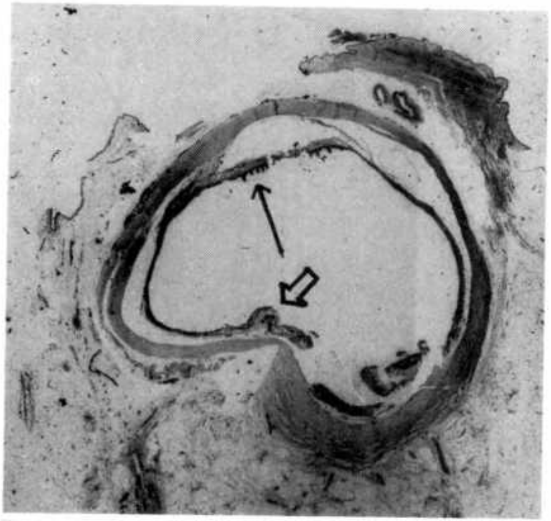

Fig. 4 *Section of the eyeball showing anterior insertion of short ciliary processes* (long arrow), *and dysplastic retina in the posterior pole* (open arrow). *(Haematoxylin and eosin).*

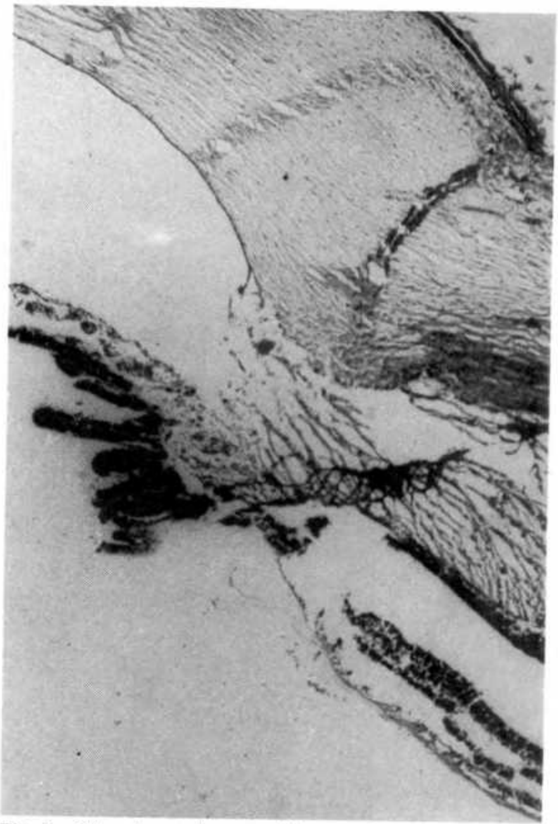

Fig. 5 *Chamber angle covered by mesodermal tissue. Anterior insertion of ciliary processes. Congested iris. Very short pars plana of the ciliary body with sudden transformation into retina. (Haematoxylin and eosin, ×50).*

The angle of the anterior chamber was not open at all and Schlemm's canal could not be recognised. Mesodermal tissue covered the area to be trabeculum (Fig. 5). Histological study of the lens showed nothing abnormal.

Discussion

Cyclopia, which is an anomaly of organogenesis of the eye, results from arrest of development of the anterior end of the neural plate.[1 14 15] Thus cyclopia is always associated with abnormalities of the brain. The anomaly was classified by De Myer *et al.*[16] as the

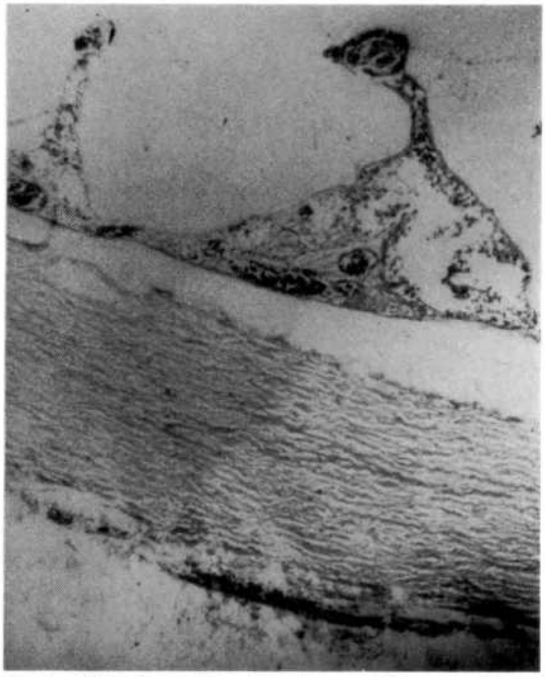

Fig. 6 *Retinal projection into vitreous. (Haematoxylin and eosin, ×50).*

most extreme form of holoprosencephaly when they graded the disorders in which there is impaired midline cleavage of the embryonic forebrain. The same authors correlated the appearance of the face and the type of brain malformation in holoprosencephaly. Confirming that view, Torczynski *et al.*[1] reported data based on the analysis of a series of 35 cases of synophthalmia—cyclopia.

In the early development of the embryo certain groups of cells (anlage) differentiate into masses destined to give rise to definite organs or tissues. Injury or abnormality of these specialised cell masses at certain critical stages during their development can result in congenital malformation of the organs or tissues.[14]

The two chief mechanisms are defective inheritance and an unfavourable environment. These mechanisms must act on the embryo at or before the determination of the eye anlage, and continuously thereafter by altering the interaction between the anlage and the surrounding endomesoderm.[14] This action must take place before the first manifestation of the bilateral nature. In the human embryo this is at 1·8 mm stage or during the third week of gestation.

Our case was a female cyclopian monster born to first cousin parents. Seventeen of the 35 cases reported by Torczynski *et al.*[1] were females, nine were males, and in the remaining nine the sex was not stated. The literature supports the predominance of cyclopean female monsters. Cohen and Gorlin[11] reported a case and considered the genetic aspects of holoprosencephaly. In addition to their case with parenteral consanguinity they mentioned another two cases reported by Klopfstock in 1921 and Grebe in 1954. To our knowledge our case is the fourth to be reported.

Francois[17] suggested that cyclopia is a lethal autosomal recessive trait. Gorlin *et al.*[18] suggested that some cases of holoprosencephaly may be caused by an autosomal recessive gene in an individual with normal karyotype, and suggested that the responsible gene is located on the short arm of chromosome 18.

In our case chromosomal studies were normal. Karseras and Laurence[19] concluded that normal chromosomal studies do not necessarily exclude an underlying chromosomal disorder, since this may not have been discovered by earlier methods and may still escape detection by current methods.

Jaschevatzky *et al.*[5] discussed the presence of extracephalic and extrafacial malformations in cyclopia with trisomy-D. They reported detailed information about these malformations in each case in the literature known until 1976 with chromosomal aberrations. In cases with normal karyotype there was no information about extracephalic malformations. In our case the only extracephalic defect was persistent patent ductus arteriosus.

A classification of two main aetiological groups was suggested by Taysi and Tinaztepe.[20] In the first group there were only cephalic malformations and the karyotype was normal. In the second group there were cephalic as well as extracephalic malformations with anomalous karyotype, mostly trisomy-D. Our case with patent ductus arteriosus and normal karyotype does not seem to belong to any of the aforementioned groups, so the discussion is left open at this point.

The environmental factors known to cause cyclopia in clinical practice and in experimental investigations are numerous. Mollica *et al.*[3] reported six cases of cyclopia in which the mother was exposed to drugs or to other potentially teratogenic environmental factors during organogenesis. These factors were ionising radiation, contraceptives, viraemia plus cortisone and salicylate, rubella vaccine, antibiotics, and amidopyrine. Other known factors are lithium, magnesium, veratrum alkaloids (in ruminantes) vinca alkaloids, and vitamin A in rats.[1]

In our case the pregnancy developed under an intrauterine device containing copper, which was inserted one week after the last menstrual period; the mother was also given drugs during organogenesis (tranexamic acid and ampicillin). There is no mention in the literature of cases of cyclopia after tranexamic acid ingestion, but antibiotics were incriminated by Mollica *et al.*[3] We found no reports of intrauterine devices as the possible cause of cyclopia.

On histopathological examination of the eyeball the main finding was the presence of a well formed globe in which malformations are prominent: hypercellular cornea, non-cleavage anterior chamber angle, lack of dilator muscle and endothelial cells of the iris, anterior insertion of the ciliary body, anomalous transformation of ciliary pigment epithelium into retinal pigment epithelium, choroidal colobomas, disorganisation and dysplasia of the retina with rosette formation, lack of retinal ganglion cells and nerve fibres, and projection of retinal tissue into the vitreous and into the sclera.

Most of these malformations were discussed or mentioned by other authors[1 2 14] in cases of cyclopia-synophthalmos. The anterior insertion of the ciliary body processes (Figs. 4 and 5) was discussed by Barishak[21] in the human embryo and in avian and mammalian eyes but has not previously been reported in cyclopian eyes. Barishak concluded that anterior insertion of the ciliary processes is normally found in the human embryo during the second trimester of pregnancy. In the third trimester the ciliary processes move backward posterior to the apex of the angle of the anterior chamber, and this is the result of a difference in growth rate of the neuroepithelial and mesodermal layers at the ciliary body region.

References

1 Torczynski E, Jacobeic FA, Johnston MC, Font RL, Madewell JR. Synophthalmia and cyclopia: a histologic, radiographic and organogenetic analysis. *Doc Ophthalmol* 1977;**44**:311-78.

2 Duke-Elder S. Anomalies of fusion. *System of ophthalmology.* St Louis: Mosby, 1963; **3:** 429–49.

3 Mollica F, Pavone L, Sorge G. Maternal drug ingestion and cyclopia. *J Pediatr* 1981; **98:** 680.

4 Benawra R, Mangurten HH, Duttell DR. Cyclopia and other anomalies following maternal ingestion of salicylates. *J Pediatr* 1980; **96:** 1069–71.

5 Jaschevatzky OE, Goldman B, Georghion P, Grunsterin S, Pevzner S. Trisomy-D in a cyclops with cardiovascular defects. *Acta Obstet Gynecol Scand* 1976; **55:** 73–6.

6 Arakaki DT, Waxman SH. Trisomy-D in cyclops. *J Pediatr* 1969; **74:** 620–5.

7 Batts JA, Punnet HH, Valdes-Dapena M, Coles JW, Green WR. A case of cyclops. *Am J Obstet Gynecol* 1972; **112:** 657–61.

8 Cohen MM. Chromosomal mosaicism associated with a case of cyclopia. *Pediatrics* 1966; **69:** 793–8.

9 Halbrecht I, Kletzky O, Komlos L, Lotker M, Gersht N. Trisomy-D in cyclops, a case report. *Obstet Gynecol* 1971; **37:** 391–3.

10 Khudr G, Olding L. Cyclopia. *Am J Dis Child* 1973; **125:** 120–2.

11 Cohen MM, Gorlin RJ. Genetic consideration in a sibship of cyclopia and clefts. *Birth Defects* 1969; **5:** 113–8.

12 Zimmer EZ, Divon MY, Halperin M, Peretz BA. Cyclopia with trisomy-D. *Eur J Obstet Gynecol* 1982; **13:** 215–9.

13 Towes HA, Jones HW Jr. Cyclopia in association with trisomy-D and gonadal agenesis. *Am J Obstet Gynecol* 1968; **102:** 53–6.

14 Barber AL, Muelling RJ Jr. Cyclopia with complete separation of the neural and mesodermal elements of the eye. *Arch Ophthalmol* 1950; **43:** 989–1003.

15 Adelman HB. The problem of cyclopia. *Q Rev Biol* 1936; **11:** 161–82, 248–304.

16 De Myer WE, Zeman W, Palmer CG. The face predicts the brain: diagnostic significance of median facial anomalies for holoprosencephaly. *Pediatrics* 1964; **34:** 256–263.

17 Francois J. *Heredity in ophthalmology.* St Louis: Mosby, 1961: 173–6.

18 Gorlin RJ, Yunis J, Anderson VE. Short arm deletion of chromosome 18 in cebocephaly. *Am J Dis Child* 1968; **115:** 473–6.

19 Karceras AG, Laurence KM. Eyes in arinencephalic syndromes. *Br J Ophthalmol* 1975; **59:** 462–73.

20 Taysi K, Tinaztepe K. Trisomy-D and the cyclops malformation. *Am J Dis Child* 1972; **124:** 710–3.

21 Barishak YR. Development of the angle of the anterior chamber of the eye in animals and human embryos. *Metab Ophthalmol* 1978; **2:** 269–73.

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Changing pattern of childhood blindness in Saudi Arabia

KHALID F TABBARA AND IHSAN A BADR

From the King Khaled Eye Specialist Hospital and Research Center, Riyadh, Saudi Arabia, and the Francis I Proctor Foundation for Research in Ophthalmology and the Department of Ophthalmolgy, University of California, San Francisco, USA

SUMMARY We studied 187 patients attending special educational institutions in Saudi Arabia who were blind before the age of 14. All patients underwent complete ophthalmological evaluation. The visual acuity in 31% of the patients was no light perception and in 58% light perception to counting fingers at 3 feet (1 m). 70% were blind before age 2. Prior to 1962 acquired diseases led to blindness in 75% of the patients. From 1962 onwards genetically determined diseases accounted for 84% of childhood blindness. 56% of this group were the product of consanguineous marriages. On the other hand in the group who acquired blindness only 14% were from consanguineous marriages ($p<0.0001$). We here describe guidelines for the prevention of childhood blindness in Saudi Arabia.

Blindness in children has been studied in different parts of the world.[1-8] In general, malnutrition and infections are major factors and frequent causes of childhood blindness in many underdeveloped and developing countries. In developed countries genetically determined causes of childhood blindness are more prevalent than nutritional or infectious causes. Socioeconomic development and governmental programmes appear to help in eliminating these causes of blindness.

Statistical data about the causes of childhood blindness throughout Saudi Arabia, however, are not available. We therefore studied the causes of blindness among 187 Saudi students and assessed the changing pattern in the causation of childhood blindness in Saudi Arabia.

Subjects and methods

Subjects. One hundred and eighty-seven students attending two schools for the blind in Riyadh, Saudi Arabia, were examined. Students came from different parts of the country seeking education, which is subsidised by the Saudi government. We obtained individual histories from the medical charts at the schools, from the students themselves, or from parents.

Medical evaluation. We assessed the visual acuity and examined each student. All students underwent complete ophthalmological evaluation, including biomicroscopy and ophthalmoscopy. Ancillary ophthalmological testing, such as visual fields, A and B scan, visual evoked response (VER), electro-oculography (EOG), and electroretinography (ERG) were performed when indicated. In addition, students were seen by a paediatrician or an internist, depending on their age. Further laboratory testing was performed to corroborate the clinical findings and confirm the clinical impression. All examinations were carried out at the King Khaled Eye Specialist Hospital and Research Center in Riyadh, Saudi Arabia.

Criteria for inclusion in the study. One hundred and seventy of the 187 students examined were included in the study. Those included met the following three criteria: (1) The onset of blindness had occurred prior to the age of 14 years, (2) visual acuity was 20/200 or less in the eye with the best correction, and (3) the patient was born and had resided in Saudi Arabia all of his/her life.

Statistical analysis. The χ^2 test was used for statistical analysis of the data.

Age and sex. There were 108 male and 62 female

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Table 1 *Age and sex distribution*

Age group	*Male*	*Female*	*Total*
A. <20 years	62 (59%)	43 (41%)	105
B. 20 years and over	46 (71%)	19 (29%)	65
Total	108	62	170

students. The male to female ratio was 1·7:1. Table 1 shows the age and sex distribution among the group studied. The group was divided into two subgroups: (A) patients born before 1962 (65 patients), and (B) patients born after 1962 (105 patients).

Results

Onset of blindness. Tables 2 and 3 depict the age of onset of blindness in patients born before and after 1962 respectively. Among the group born before 1962, 18% became blind before the age of 2 years and 82% after that. This is in sharp contrast to the data showing that 70% of the patients born in or after 1962 were blind before the age of 2 years.

Visual acuity. Fifty-two students (31%) had no light perception, 98 (58%) had visual acuity ranging from light perception to counting fingers at 3 feet (1 m), and 20 (11%) had a visual acuity varying between counting fingers at 3 feet (1 m) and 20/200.

Causes of blindness. Tables 4 and 5 show the causes of blindness among 163 Saudi students. The cause could not be determined among seven students; four were born prior to 1962 and three were born in or after 1962. One hundred and six students were blind from genetically determined diseases, and 57 students were blind from acquired diseases. Table 4 demonstrates the genetically determined diseases among 106 blind students. The diagnosis of genetic disorders was presumptive and based on the medical and family history and clinical findings.

Table 2 *Age of onset of blindness in patients born before 1962*

Age of onset (years)	*Male*	*Female*	*Total*
<2	9	3	12 (18%)
2–8	19	12	31 (48%)
9–14	18	4	22 (34%)
Total	46 (71%)	19 (29%)	65 (100%)

Table 3 *Age of onset of blindness in patients born in or after 1962*

Age of onset (years)	*Male*	*Female*	*Total*
<2	40	33	73 (70%)
2–8	18	9	27 (26%)
9–14	4	1	5 (4%)
Total	62	43	105 (100%)

Table 4 *Genetic disorders among 106 blind students*

Genetic disorders	*Born before 1962 No. (%)*	*Born in or after 1962 No. (%)*
Congenital cataract	6 (38)	30 (33)
Primary pigmentary degeneration	1 (6)	26 (29)
Congenital glaucoma	4 (25)	14 (16)
Leber's congenital amaurosis	—	7 (8)
Other causes	5 (39)	13 (15)
Total	16 (100%)	90 (100%)

Congenital cataract was the most frequently encountered genetic cause of blindness among both the group of students born before 1962 and those born in or after 1962. The evidence that the congenital cataract was genetically determined was presumptive and based on the family history, the inheritance pattern, and the absence of associated clinical findings that would suggest an in-utero acquired infection, a prenatal or perinatal disorder. Table 5 depicts the acquired causes of blindness before and in or after 1962. Among students who were born before 1962 91% of the causes of blindness were due to bilateral keratitis, subsequent corneal scarring, and/or perforation. Keratitis was due to bacterial corneal ulcers in 23, smallpox in 16, and measles in two students. No cases of smallpox leading to blindness could be detected in the group of students born after 1962. It is interesting that genetically determined causes accounted for blindness in 16 (25%) of 65 students born before 1962 and 90 (86%) out of 105 students born in or after 1962. There is a marked difference, in that acquired diseases (corneal infections, etc.) accounted for 60% of the causes of childhood blindness in the group born before 1962 and only 11% of the group born after 1962 ($p<0{\cdot}0001$).

Family data. Among the students examined 67 out of 163 were the products of consanguineous marriages. Table 6 shows the correlation between the causes of childhood blindness and consanguinity among the parents. 56% of the students with genetically determined diseases were the product of consanguineous marriages compared with 14% in the students with acquired disorders.

Table 5 *Acquired causes of childhood blindness in Saudi Arabia*

Acquired cases	*Born before 1962 No. (%)*	*Born in or after 1962 No. (%)*
Bacterial keratitis	25 (56)	4 (33)
Smallpox	16 (36)	0 (0)
Accidents	2 (4)	7 (58)
Other	2 (4)	1 (8)
Total	45 (100)	12 (100)

Table 6 *Childhood blindness and parents' consanguinity*

	No.	*Consanguinity**
Genetically determined	106	59 (56%)
Acquired	57	8 (14%)
Total	163	67

*$p<0{\cdot}0001$.

Discussion

As our study shows, most of these blind students are males. This is due to cultural factors. For instance, families give priority to boys for educational opportunities, and avoid sending their girls away from home.[9] Furthermore, certain diseases such as X-linked retinitis pigmentosa may lead to an increase in blindness among males.

The data obtained in this study indicates a changing pattern in the causes of childhood blindness in Saudi Arabia. There is a relative decrease in the incidence of corneal infections leading to blindness. After 1962 no smallpox keratitis leading to blindness could be detected. This is probably due to mass vaccination which has eradicated smallpox. In addition there was a corresponding decrease in the incidence of bacterial corneal ulcers as a cause of corneal perforation, endophthalmitis, and loss of the globe. This could be related to the recent economic improvements and to the dedication of the Saudi government in the delivery of health care.

Infectious trachoma is still highly prevalent in Saudi Arabia[10,11] and may lead to serious ocular complications and blindness in the adult population. In many instances we found evidence of active trachoma among the examined children, but trachoma was not incriminated as a direct cause of blindness in this age group. Childhood trachoma may lead to scarring of the palpebral conjunctiva, causing entropion and trichiasis. Persistent rubbing of the cornea by the eyelashes can lead to corneal abrasions, ulcerations, and secondary bacterial ulcers in adult life.

In the past two decades there has been an apparent decrease in the acquired causes of childhood blindness and a relative increase in the incidence of genetically determined causes. The preponderance of genetic diseases in the group born in or after 1962 coincides with reports from developed countries[3,4] and appears to be different from other African, Asian, and Central American countries.[6–8] Table 7 shows a comparison of the causes of childhood blindness among four countries. The mode of inheritance of the majority of genetic disorders in this group were autosomal recessive. The incidence of parental consanguinity among blind students with genetic diseases was significantly higher than among the parents of the students in the group with acquired diseases ($p<0{\cdot}0001$). It is a common and accepted tradition for marriages to be consanguineous. Marriages among cousins in Saudi Arabia are common and encouraged by the Arab family. In spoken Arabic the words for spouse and father-in-law are frequently interchangeable with cousin and uncle.

The segregation of blind students in special educational institutions provides a convenient framework for the study of childhood blindness. Such a study suffers from certain limitations, however. It excludes certain groups of patients who may suffer from blinding ocular disorders. For example, the mentally retarded, the partially sighted, the one-eyed, the deaf, and children of preschool age are not represented. Although the group investigated may not be representative of all blind children in Saudi Arabia, this study was successful in producing a balance sheet for the causes of childhood blindness in the Kingdom and in demonstrating a change in the pattern of causation. The overall rate of blindness cannot be assessed in this study. We therefore believe that a large-scale, statistically planned survey is indicated to evaluate the rate of childhood blindness in Saudi Arabia.

Table 8 shows suggested guidelines for the prevention of childhood blindness in Saudi Arabia. Eye examination at birth is of great importance in the prevention of blindness in childhood. The eye examination should be carried out by a paediatrician who

Table 7 *Comparison of childhood blindness in four countries*

Aetiology	*England and Wales[3] (%)*	*Cyprus[1] (%)*	*Lebanon[2] (%)*	*Saudi Arabia: present study (%)*	
				Before 1962	*In or after 1962*
Hereditary	50	79	77	25	84
Prenatal	6	4	1	3	1
Perinatal	33	2	2	0	1
Postnatal	11	15	20	66	11
Unknown	—	—	—	4	3

Table 8 *Guidelines for the prevention of childhood blindness in Saudi Arabia*

1. Eye examination at birth
2. Screening of preschool children
3. Early management of congenital cataract
4. Early management of glaucoma
5. A comprehensive programme of religious and governmental intervention to discourage marriage between persons having the same grandfather or grandmother
6. Genetic counselling
7. Vaccination for measles and rubella
8. Early detection and management of bacterial corneal ulcers
9. Mass treatment for trachoma

is well informed about neonatal ocular disorders. Early detection of congenital cataracts and glaucoma should be followed by prompt treatment. Children with congenital cataracts should undergo surgical intervention and close postoperative follow-up for visual rehabilitation with corrective lenses. Similarly, congenital glaucoma should be treated early to prevent irreversible damage to the optic nerve. Screening of preschool children is aimed at the early detection of certain disorders such as ocular deviations and amblyopia. On the other hand consanguinity among married couples is a serious phenomenon in Saudi Arabia. This may explain the high prevalence of autosomal recessive disorders. Consanguineous marriages should be discouraged by systematic public education campaigns with the support of the religious authorities.

At present there are nine institutions for the visually handicapped in Saudi Arabia. The education of the children and young adults attending these institutions is fully subsidised by the Saudi government. Students are taught courses by braille and they are trained to acquire proficiency in certain manual skills such as pottery, handicrafts, weaving, etc. They are also trained to cope with their environment without help from the outside.

This study was supported by a grant from the King Khaled Eye Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

References

1 Merin S, Lapithis AG, Horovitz D, Michaelson IC. Childhood blindness in Cyprus. *Am J Ophthalmol* 1972; **74:** 538–42.

2 Baghdassarian SA, Tabbara KF. Childhood blindness in Lebanon. *Am J Ophthalmol* 1975; **79:** 827–30.

3 Fraser GR, Friedman AI. *The causes of blindness in childhood. A study of 766 children with severe visual handicaps.* Baltimore: Johns Hopkins Press, 1967: 1–245.

4 Fraser GR. Causes of severe visual handicap among school children in Southern Australia. *Med J Aust* 1968; **i:** 615–20.

5 Macdonald AE. Causes of blindness in Canada. *Can Med Assoc J* 1965; **92:** 264–79.

6 Quere MA. Ocular complications of measles as a major cause of blindness in children in tropical countries. *Ophthalmologica* 1964; **148:** 107–20.

7 Olurin O. Etiology of blindness in Nigerian children. *Am J Ophthalmol* 1970; **70:** 533–40.

8 Sommer A, Quesada J, Doty M, Faich G. Xerophthalmia and anterior-segment blindness among preschool-age children in El Salvador. *Am J Ophthalmol* 1975; **80:** 1066–72.

9 Badr IA, Qureshi IH. Cause of blindness in the Eastern Province blind schools. *Saudi Med J* 1983; **4:** 331–8.

10 Tabbara KR, Bobb AA. Lacrimal system complications in trachoma. *Ophthalmology* 1980; **87:** 298–301.

11 Badr IA, Qureshi IH. Trachoma in Saudi Arabia. *Saudi Med J* 1982; **3:** 53–6.

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Obituary

Manuel Lederman MB, BS, FFR, DMRE

Manuel Lederman, who died on 27 June 1984, was born in 1911 and received his medical training at the Westminster Hospital, where he won the Sturges Prize for clinical medicine and the Hanbury Prize for diseases of children. He qualified in 1935. His interest in radiotherapy was stimulated by Sir Stanford Cade, and his first appointment was that of resident medical officer to the Radium Annexe of the Westminster Hospital. Two years later he was appointed assistant radium therapist at the Royal Cancer Hospital (subsequently the Royal Marsden Hospital), where he spent the remainder of his career. His initial interests were gynaecological cancer and more especially head and neck cancer. He developed new techniques of irradiation of tumours of the head and neck using the newly installed teleradium units.

Early in his career Dr Lederman developed an interest in the treatment of diseases of the eye and orbit by ionising radiation. He took charge of the *x*-ray Department of Moorfields Eye Hospital in 1941, remaining in charge until 1948, when all radiotherapy was transferred from Moorfields to the Royal Cancer Hospital. He remained as honorary consultant radiotherapist to Moorfields Hospital and established a flourishing joint eye tumour clinic at both hospitals. He pioneered many techniques of radiotherapy of eye conditions, including the strontium-90 plaque for superficial irradiation of the cornea and conjunctiva, introduced in 1954. He had a special interest in the conservative treatment of epibulbar melanoma; his final paper describing his experience of the treatment of these tumours over a period of 31 years appeared posthumously in the *British Journal of Ophthalmology* last year.

He always emphasised the art rather than the science of radiotherapy. Nevertheless he had an unrivalled knowledge of the anatomy and physiology of the head and neck, which he applied to understanding the origin and spread of malignant tumours, enabling him to tailor radiotherapy technique to the individual patient without the aid of the more sophisticated imaging and technology now available. He was a fine teacher. As he saw each patient in his clinic he would expound articulately and succinctly on the natural history of the disease before him and on the rationale of the treatment in use, usually to an audience comprising not only his own juniors and students but also visiting doctors from many parts of the world. He was in great demand as a lecturer and contributor to scientific meetings. His presentations were invariably carefully prepared, well rehearsed, and fluently delivered. In discussion at meetings he could be a potent adversary, quick to spot the flawed argument or the unsubstantiated claim. He rapidly built up a reputation as a clinician which attracted patients from many countries. After his retirement from hospital practice in 1977 his advice continued to be sought by colleagues and patients, and he remained in active practice until a few weeks before his death.

His talents brought him many honours in the field of radiotherapy and oncology. The British Institute of Radiology awarded him the Roentgen Award in 1956 and the Barclay Medal in 1972 for his contributions to the *British Journal of Radiology*. The Royal College of Radiologists awarded him the Knox Medal in 1974 for a masterly exposition of the behaviour of head and neck cancer entitled 'The oncology of breathing and swallowing.' The section of laryngology of the Royal Society of Medicine awarded him the Harrison Prize in 1976 for his outstanding contributions to the management of head and neck cancer. His professional standing was acknowledged by his election as president of the Section of Radiology of the Royal Society of Medicine in 1967, of the Section of Oncology in 1972, and of the Association of Head and Neck Oncologists of Great Britain in 1974. His generosity was shown by his endowing the Leah Lederman lecture at the Royal Society of Medicine in memory of his mother, and in his presenting the furnishings for the council chamber of the Royal College of Radiologists.

Dr Lederman was a splendid host. Many of his friends and colleagues and visiting doctors from abroad have enjoyed his warm hospitality at his home in Montpelier Square. He was a lover of art, and his home contained a magnificent collection of paintings. He will be sadly missed in the spheres of both radiotherapy and ophthalmology. Our sympathy is extended to his wife Vera, who was his professional colleague for many years. JMH

Book review

Color and Fluorescein Angiographic Atlas of Retinal Vascular Disorders. By DAVID ORTH. Pp. 411. £160·00. Williams and Wilkins: London. 1984.

This is a very well illustrated, comprehensive colour atlas of retinal vascular disease. There are accompanying fluorescein angiograms of high quality and, in appropriate sections, some excellent coloured diagrams explaining the pathogenesis of the various vascular conditions. Many of the photographs are accompanied by short clinical descriptions, which I found useful. However, there was little prognostic forecasting or follow-up data given. There is quite a lot of reduplication of the same retinal vascular conditions, and this, I think, makes the book too long. Its price puts it out of the reach of the majority of ophthalmologists, and not many ophthalmic libraries could afford to invest in it.

RONALD J MARSH

Correction

In the paper by W E Gillies and Anne Hughes entitled Results in 50 cases of strabismus after graduated surgery designed by A scan ultrasonography (*Br J Ophthalmol* 1984; **68:** 790–5) an error occurred on p. 794, last paragraph. The second sentence should read: 'We prefer to avoid recessions greater than 0·2 of muscle length . . .' (not 0·2 mm as printed). The 0·2 refers to a decimal estimate of muscle length such as is used in estimating cupping of the optic disc.

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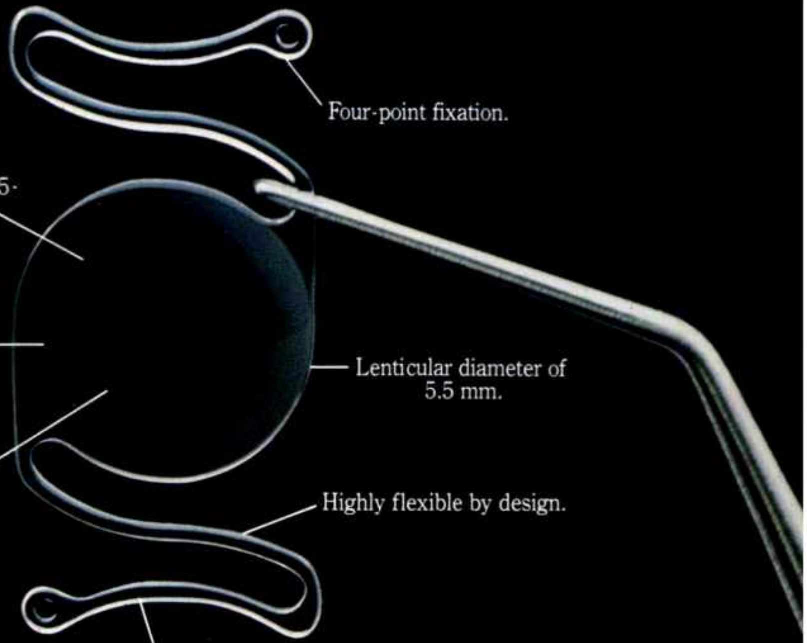

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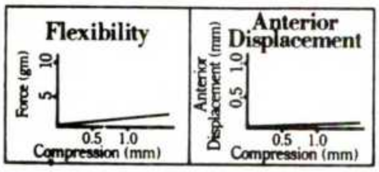

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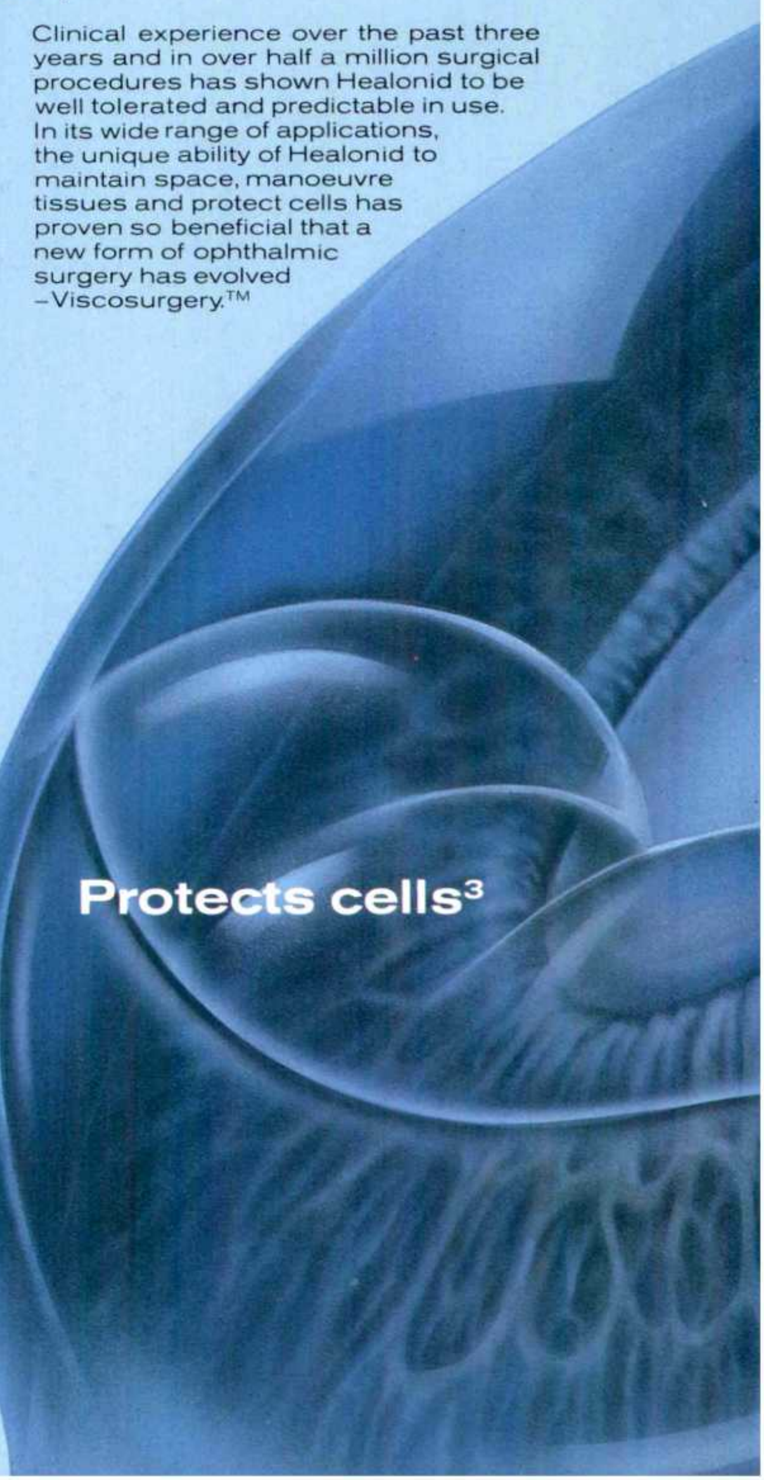

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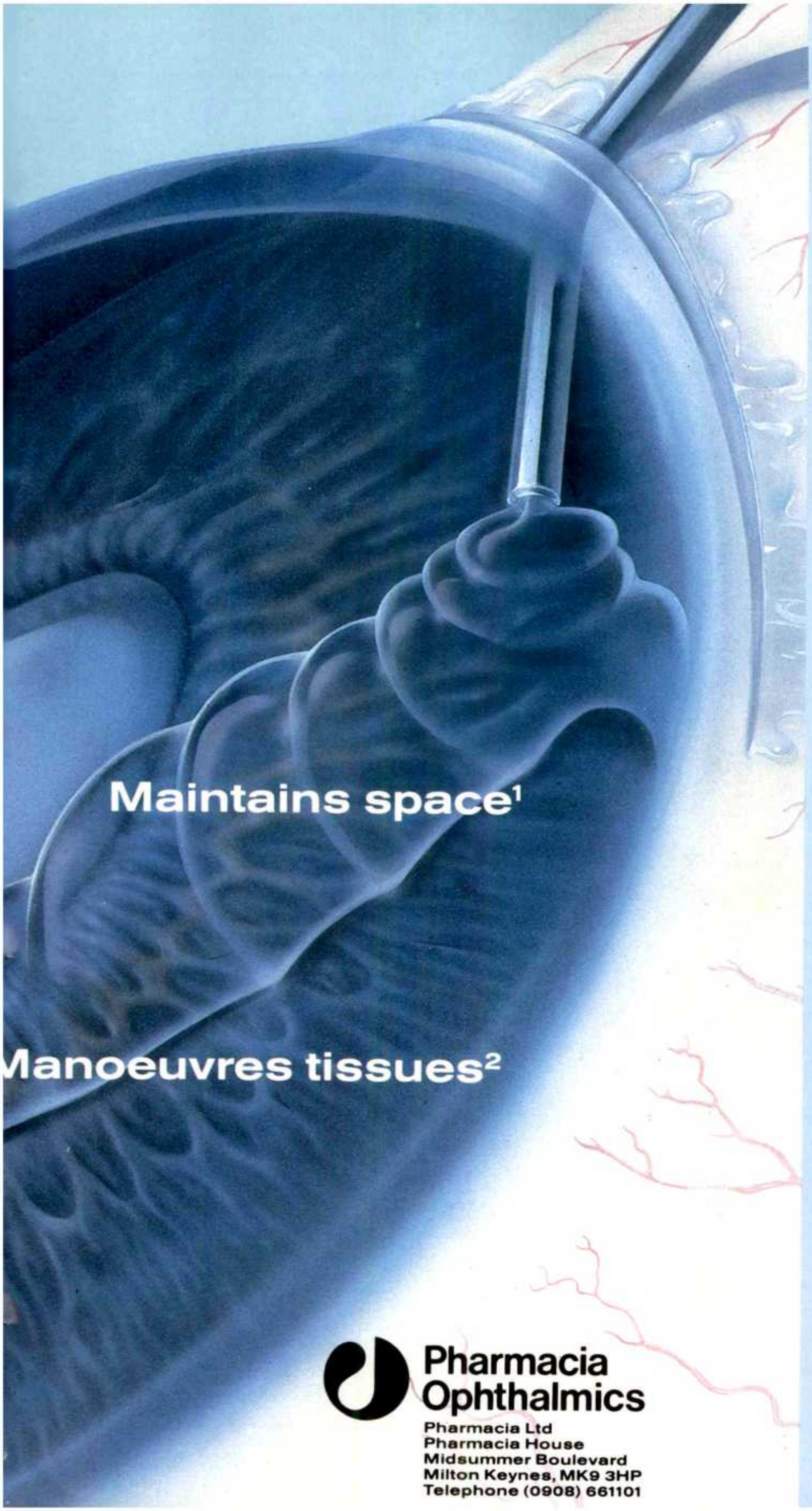

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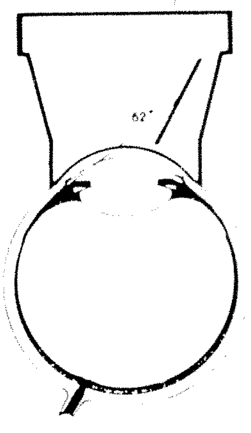

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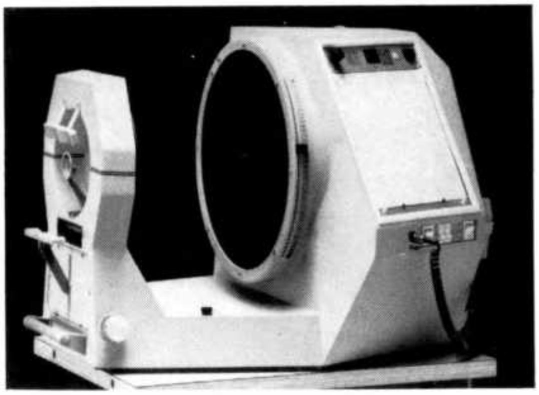

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The eye and the seatbelt in Wessex

N F HALL,[1] A M DENNING,[1] A R ELKINGTON,[1] AND P J COOPER[2]

From the Departments of [1]Surgery and [2]Social Statistics, University of Southampton, Southampton SO9 5NH

SUMMARY The records of all 373 patients undergoing surgery for perforation of an eye at the 10 eye units in the Wessex Regional Health authority (except the Isle of Wight) during February 1980 to January 1984 were examined. There were 86 admissions as a result of road traffic accidents (RTAs), and 287 admissions arising from other accidents. The estimated annual incidence of perforating eye injuries as a result of RTAs has decreased by 73% following legislation for the compulsory wearing of seatbelts by drivers and front seat passengers. There is no evidence that this abrupt fall in the incidence of injury can be satisfactorily attributed to any other factor.

Every eye Surgeon practising in the United Kingdom will have seen patients whose eyes were damaged in road traffic accidents (RTAs). Canavan *et al.*, reporting the results of a 10-year survey of eye injuries in Northern Ireland, found that nearly a third (30·2%) of perforating eye injuries stemmed from such accidents. The victims are characteristically in their 20s or 30s, and their eyes are usually damaged as their heads move downwards on to the jagged lower remnants of a shattered, toughened windscreen.[2] This has lead Du Fourmentel and Mouly[3] to use the graphic phrase 'the guillotine of the windscreen.' This mechanism explains why these patients so often have a horizontal band of facial lacerations, and it also explains perforation of both eyes.[4]

Despite the great advances in microsurgical repair of such eyes the visual outcome is frequently disappointing. Lavergne[5] reports that in one series of 97 patients with perforated eyes 29% of eyes eventually lost all 'functional vision.' In Canavan and colleagues' study,[1] the most frequent reason for an eye being excised was damage incurred in an RTA (27·8% of all enucleations).

Australia led the way in countering many types of RTA injuries by the introduction of seatbelt legislation in 1971.[4] Over the succeeding years a marked reduction in injuries has been reported from many countries.[6] Legislation relating to the compulsory wearing of seatbelts by both driver and front seat passenger came into force in the United Kingdom on 31 January 1983 and is due to be reviewed by Parliament early in 1986.

Blake[7] has reported that many people working in eye departments have recently noted an apparent decrease in the number of patients with eyes perforated in RTAs. We set up this study to discover the extent of this suspected trend, for, as Mackay[8] has pointed out, the final test of the effectiveness of the legislation is the change in the number of casualties.

Three major considerations influenced the choice of the population for the study. First, we chose to investigate perforating eye injuries rather than lesser ocular injuries because of their worse visual prognosis.[9] Secondly, we aimed to identify all cases in the study period. Thirdly, we needed to choose a study period long enough for the pattern of cases over time to be clear but short enough for other factors influencing the incidence rate of injuries to remain fairly stable. The period used is three years before and one year after the introduction of legislation—that is, 1 February 1980 to 31 January 1984.

Material and methods

In each of the 10 eye units on the mainland of the Wessex Regional Health Authority (RHA) the theatre books were used to identify all cases of perforating eye injuries. In each case the patient's name, unit number, and date of operation were used to trace the corresponding medical records. These records enabled all the cases of perforating eye injuries to be identified and subsequently divided into those resulting from an RTA and those from other causes. For RTAs we recorded the date of the accident, the age and sex of the patient, and other medical information.

Additional data have been obtained or derived

Correspondence to Mr A R Elkington, Southampton Eye Hospital, Wilton Avenue, Southampton SO9 4XW.

Table 1 *Eye injury and related data for February 1980 to January 1984 inclusive*

Accident year February-January	*Cases with penetrating eye injury*		*Population (m) of Wessex RHA* aged 15 and over*	*Index of average daily vehicle flow GB (1977=100)‡*
	RTA	*Non-RTA*		
1980–1	34	70	2·20	106
1981–2	24	75	2·22	105
1982–3	21	70	2·24	112
1983–4	7	72	2·26	117

**Statistical year book.* Chapter A. Winchester: Wessex RHA, 1984.
†Hampshire Police authority data (available on request).
‡Department of Transport. *Transport statistics*, Great Britain. HMSO: 1972–82. 1983–4 figure estimated from Press Notice.
§Estimated from Table 2.20 Transport Statistics, Great Britain. HMSO: 1972–82; and data supplied by University of Birmingham Accident Research Unit.
‖Department of Transport Press Notice 2 dated 12th January, 1984.
‖Government Statistical Service. Press Notice 2. *Road casualties in third quarter of 1983*. London: Department of Transport. 1984.

from published sources. These include population data for the Wessex RHA; the number of RTAs in Hampshire divided into those involving fatal and serious injury, slight injury, and vehicle damage only; the proportion of cars and light vans in Great Britain having laminated windscreens; and the proportion of all front seat occupants wearing seatbelts.

Results

Table 1 shows that perforating eye injuries in RTAs fell from an average of 26·3 per annum during February 1980 to January 1983 to seven in the year immediately following the introduction of seatbelt legislation. This was a fall of 73% in the estimated annual incidence rate. In contrast over the same periods injuries not related to RTAs averaged 71·7 and 72 respectively. The proportion of perforating eye injuries caused by RTAs dropped significantly ($\chi^2=14{\cdot}45$, df=3, $p<0{\cdot}01$). The adult population of the Wessex RHA and the index of vehicle flow on roads in Great Britain (an amalgam of the number of vehicles and distance travelled by each vehicle) increased slightly over the study period. The annual number of accidents involving fatal or serious injury in Hampshire (a county typical of the mainland Wessex region) decreased by some 11% from 1980–3 to 1983–4. This contrasted with the sharp increase in the number of accidents with damage only to vehicles in 1983–4 and an increase during the latter half of the study period in the total number of accidents. The proportion of all cars and light vans with laminated windscreens increased steadily over the period. In contrast the proportion of front seat occupants wearing seatbelts rose gently prior to legislation, after which it increased very sharply.

Discussion

We decided that scrutiny of theatre registers was the best method of identifying cases of perforating eye injury because patients with such injuries are virtually always dealt with surgically. This involved examining the records of the 10 specialist eye units and those of the general theatres where patients were sometimes treated in an emergency.

We noted not only cases of repair of a perforation but also cases of an intraocular foreign body; the removal of sutures; enucleation and evisceration; and any instance where the entry in the register did not make clear what operation had been carried out. We listed 1201 entries in this way. We were unable to trace the notes for 39 (3·2%) of cases. However, these omissions were spread equally over the four years in question and hence do not lead us to suspect that any bias has been introduced into our study.

This system of retrieval also gave us the number of non-RTA perforating eye injuries. Reference to column 3 of Table 1 shows that these numbers remained steady throughout the four years. With no known change in the factors causing non-RTA injuries this is the expected pattern, and it supports the hypothesis that data recording and retrieval have been consistent over the study period.

Column 2 of Table 1 shows an abrupt drop in eye perforations coinciding with the introduction of seatbelt legislation. This could be attributed either to a change in the population exposed to risk of accidents giving rise to these injuries or to a change in the nature and circumstances surrounding each accident or a combination of these changes.

The magnitude of the population exposed to the risk of an RTA leading to a perforating eye injury has remained relatively stable over time. The adult

RTAs in Hampshire† involving			Estimated % cars and light vans with laminated screens in Great Britain§	Estimated % of front seat occupants wearing belts‖
Fatal and serious injuries	Slight injuries	Vehicle damage only		
2481	4414	8860	25	30
2483	4392	8692	29	30
2468	4870	9346	34	40
2207	4959	10 153	41	94

population (column 4) has grown by only an estimated 20 000 in some 2·2 million each year. The index of vehicle flow on roads in Great Britain (column 5) has risen by about 10% over the period. In a similar way the annual number of RTAs in Hampshire (columns 6, 7, and 8) has increased by about 10%. Thus the accident rate has remained relatively stable over the study period. We also note the significant change after the introduction of legislation in the distribution of accidents by the severity of the injuries sustained ($\chi^2=93{\cdot}04$, df=6, $p<0{\cdot}01$). Fatal and serious injuries (column 6) declined by 11%, accidents involving damage to vehicle only (column 8) increased by 9%, with a 2% increase in the number of accidents involving slight injuries (column 7). These patterns for Hampshire accord with those reported for Great Britain.[10] The results support the hypothesis that it is a change in the nature and circumstances of the RTAs which has led to the sharp fall in fatal and serious injuries in general and perforating eye injuries in particular.

Mackay *et al.*[11] have emphasised the importance of laminated rather than toughened windscreens in the prevention of eye injuries incurred in RTAs. During the study period an increasing number of newly registered cars and light vans were fitted with laminated windscreens (rising from an estimated 45% in 1980 to an estimated 90% in 1984). The result has been an accelerating increase in the proportion of *all* cars and light vans with laminated windscreens. However, this smooth increase is not in accord with the sharp fall in perforating injuries in RTAs between the third and fourth years of the study. It may in part explain the steady fall in injuries during the three years prior to seat-belt legislation. Over the period January 1980 to January 1983 there was a slight increase in the proportion of front seat occupants wearing seatbelts (an estimated 30 to 40%). During the following year there was a dramatic rise to an estimated 94% wearing seatbelts.

We believe that there is only one explanation for the pattern observed, namely, that the compulsory wearing of seat belts is a direct cause of the dramatic reduction in the annual incidence of perforating eye injuries in road traffic accidents.

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References

1 Canavan YN, O'Flaherty MJ, Archer DB, Elwood JH. A ten-year survey of eye injuries in Northern Ireland, 1967–76. *Br J Ophthalmol* 1980; **64:** 618–25.

2 Keightley SJ. Serious eye injury from windscreen contact. *J R Soc Med* 1983; **76:** 911–6.

3 Du Fourmentel C, Mouly R. Les traumatismes de la face au cours des accidents de la route. *Mem Acad Chir (Paris)* 1969; **95:** 558–63.

4 Trinca GW, Dooley BJ. The effects of mandatory seat belt wearing on the mortality and pattern of injury of car occupants involved in motor vehicle crashes in Victoria. *Med J Aust* 1975; **i:** 675–8.

5 Lavergne G, Dereume-de Corte MT. Les perforations oculaires par fragments de pare brisé. *Rev Med Liege* 1972; **27:** 831–4.

6 Bernard-Andersen K. *Use and effects of seat-belts in 21 countries.* Oslo: Transportokonornisk Institute, 1978.

7 Blake J. Road blindness. *Br Med J* 1983; **287:** 626–7.

8 Mackay GM. Injuries from glass in motor vehicles. In: *Proceedings of the second conference on motor vehicles and motor engineering.* Sopron: 1971.

9 Soni KG. Eye injuries in road traffic accidents. *Injury* 1973; **5:** 41–6.

10 Government Statistical Service. *Road accidents and casualties in Great Britain: 3rd quarter 1983.* London: Department of Transport, 1984.

11 Mackay GM, Gloyns PF, Hayes HRM, *et al.* Some aspects of facial injuries in present day cars. In: *Proceedings of the VIIIth international technical conference on experimental safety vehicles.* Wolfsberg: 1980.

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Multiple cotton wool spots following bone marrow transplantation for treatment of acute lymphatic leukaemia*

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SUMMARY Three patients with acute lymphatic leukaemia developed visual impairment due to occlusion of small retinal vessels with multiple cotton wool spots after treatment which included whole body and skull irradiation followed by bone marrow transplantation and cyclosporin A. Withdrawal of cyclosporin A and treatment with corticosteroids was followed by recovery of visual acuity. This retinopathy and the retinal changes seen in the immunodeficiency syndrome are thought to be closely related. The possible role of cyclosporin A is discussed, though cotton wool spots and retinal haemorrhages have never been described in renal transplant patients during treatment with this drug. Withdrawal of cyclosporin A, which is highly effective in preventing graft-versus-host disease, can be fatal. Irradiation of the skull prior to bone marrow transplantation and intrathecal administration of methotrexate may be the most important factors causing the retinal ischaemic signs described here. The inclusion of an ophthalmologist in the team monitoring transplant patients would lead to increased documentation and a better understanding of this disease.

We have recently seen three patients who developed severe visual loss two to three months after bone marrow transplantation. The ophthalmoscopic substrate of this visual loss was a disseminated multifocal ischaemic retinopathy with extensive cotton wool patches and retinal haemorrhages. All three patients had received irradiation to the head in addition to whole body irradiation and had been treated with cyclosporin A to prevent graft-versus-host disease.

The heavy maintenance immunosuppression which patients with bone marrow grafts receive suggests a possible connection between this retinopathy and that observed in the 'immunodeficiency syndrome.' However, to the best of our knowledge multifocal ischaemia of the retina with multiple cotton wool spots has not yet been reported as a complication of bone marrow transplantation.

The question therefore arises whether cyclosporin A was directly or indirectly involved in the disease process. These three cases described here may also help us to understand what is going on in the retina in the immunodeficiency syndrome.

Case reports

CASE 1

A female, born on 29 March 1961.

Primary disease. Acute lymphatic leukaemia, Calla positive, diagnosed in October 1981. Induction therapy: vincristine, prednisone, daunorubicin, L-asparaginase. Complete remission in November 1981. In November and December irradiation of the skull with 2400 rads, combined with methotrexate, mercaptopurine, vincristine, and prednisone.

Bone marrow transplantation was performed on 9 March 1982 after treatment with cyclophosphamide 60 mg/kg body weight, two doses, and following irradiation of the whole body with 1000 rads. To prevent graft-versus-host disease cyclosporin A was given at a dose of 20 mg/kg body weight the day

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*Read in part at the Washington University Eye Alumni Meeting, St Louis, Missouri, 29 April 1983.

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before, 10 mg/kg on the day of transplantation, then 5 mg/kg for 11 days, 600 mg by mouth for four weeks, later reduced to 450 mg per day. The dose of cyclosporin A was reduced when the serum creatinine increased slightly and oedema of the face developed.

Eye disease. A complete eye examination performed on 26 February 1982 prior to bone marrow transplantation was normal. Three months after bone marrow transplantation the patient noted hazy vision in the right eye. A subsequent eye examination on 6 September 1982, three months after bone marrow transplantation, showed the following: Visual acuity RE 0·7–0·8 partially unaided, LE 0·8–1·0 partially unaided. With the Amsler grid a paracentral scotoma below was shown on the right side; the left eye was normal. Pupil reactions were normal. Round the disc and the macula multiple typical cotton wool spots and some haemorrhages in the nerve fibre layer were found. No sheathing of vessels and no cells in the vitreous could be found.

The patient's general health at this time was good. Blood pressure measurements were always normal apart from a single reading of 160/90 mmHg in February 1982. Hb 10·1 g/dl, leucocytes $2{\cdot}6\times10^9$/l, normal differential count, thrombocytes 168×10^9/l. There was no evidence of platelet dysfunction at this stage. Two and a half weeks later her visual acuity decreased over the course of a few days and on 29 June was RE 0·05, LE 0·2–0·3. Amsler grid: patchy central scotoma on the right and a large scotoma below fixation on the left. Fundus examination showed a great increase in the number of cotton wool spots, which were becoming confluent (Figs. 1a, b), and more intraretinal haemorrhages were evident. The arterioles were narrow, the veins dilated. Goldmann fields showed: paracentral scotoma in both eyes for I_2, I_3, and I_4. Therapy with cyclosporin A was stopped, and prednisone 100 mg/day was given for 14 days, then in lower doses. In the following weeks the cotton wool patches regressed slowly and the scotomas in the Amsler grid disappeared, though fine retinal folds and some hard exudates were still visible at the right posterior pole. Six weeks after the patient started treatment with steroids her visual acuity RE was 0·7, LE 0·9 (Figs. 2a, b).

Follow-up. The patient remained well until the end of January 1983, when paraesthesiae developed in the left arm. On 3 February the patient was admitted to hospital after the onset of a left temporal sensory hemisyndrome 1 to 2 days previously. Neither a CT scan nor an electroencephalogram (EEG) showed any definite abnormality. A sensory Jacksonian-type epilepsy was suspected. Vascular disease, such as a cortical vein thrombosis, and leukaemic infiltration were considered as possible causes.

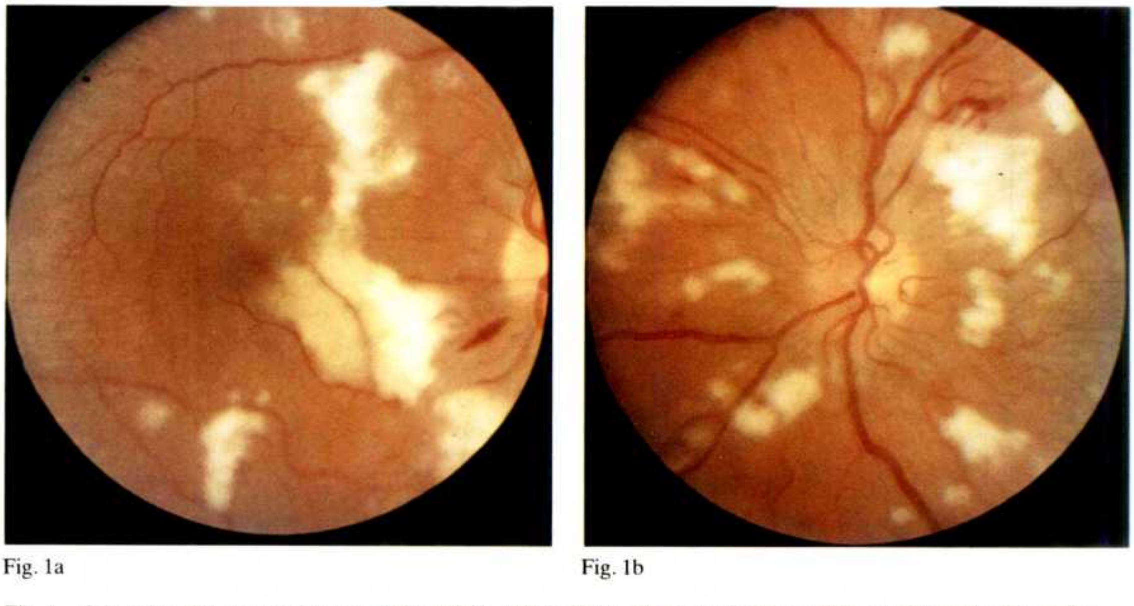

Fig. 1a

Fig. 1b

Fig. 1 *Case 1: Fundus pictures taken on 29 June 1982.* (a) *Right eye. Confluent cotton wool spots, white ischaemic oedema reaching to the foveola (VA 3/60!). Note that centrally the vessels are nowhere obscured by the white material. Flame shaped haemorrhages unrelated to the white areas. Small vessels crossing the disc margin at 8 o'clock.* (b) *Left eye shows similar changes, but disc margin more blurred than in the right eye. Macula less affected (VA 6/24).*

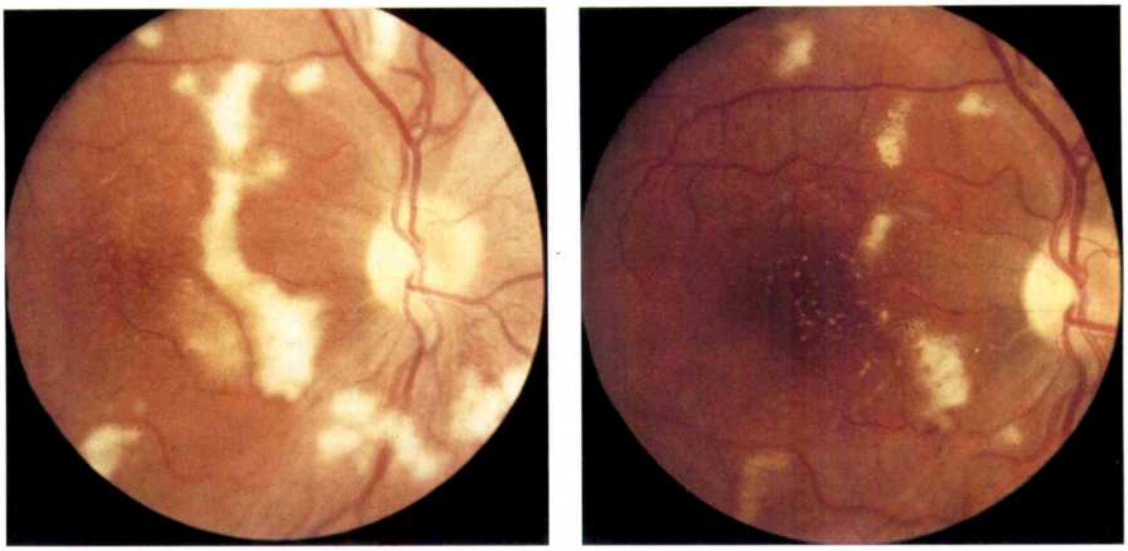

Fig. 2a

Fig. 2b

Fig. 2 *Case 1: Follow-up of right eye.* (a) *14 July: parafoveal cotton wool spots regressing; hard exudates in the macular region.* (b) *30 August: cotton wool spots are disappearing; hard exudates more pronounced.*

CASE 2

A male born on 11 March 1962.

Primary disease. Acute lymphatic leukaemia, Calla positive, was diagnosed in April 1981. Riehm's induction therapy with vincristine, prednisone, daunorubicin, L-asparaginase, cyclophosphamide, mercaptopurine, and cytarabine was given. In May 1981 irradiation of the skull with 2400 rads was performed. Methotrexate was given intrathecally. Despite maintenance therapy with methotrexate and mercaptopurine the patient relapsed in September 1981. Again induction with vincristine, prednisone, and doxorubicin (Adriamycin) was followed by maintenance therapy with doxorubicin, vincristine and cyclophosphamide. After treatment with cyclophosphamide 60 mg/kg body weight for two days whole body irradiation with 1000 rads and bone marrow transplantation were performed on 27 February 1982. To prevent graft-versus-host disease cyclosporin A at a dose of 20 mg/kg body weight was given the day before transplantation, 10 mg/kg on the day of transplantation, and for four days thereafter, followed by 5 mg/kg for three days, then a reduction to 200 mg/day. From the 41st day 800 mg/day was given orally.

Eye disease. An eye examination was performed on 15 April 1982 prior to bone marrow transplantation. Visual acuity was RE 1·0–1·2, LE 1·0–1·2; fundus RE normal, LE small round haemorrhages in the region of the inferotemporal vascular arcade. Eight days after bone marrow transplantation the patient noted a brief disturbance of accommodation. Because he complained of visual loss, another eye examination was performed on 5 August 1982. Visual acuity was then RE 1·0, LE 0·1. In the RE fine haemorrhages at the margin of the disc and cotton wool spots were noted, but the macula was normal. In the LE the optic disc was normal, but haemorrhages and cotton wool patches were seen elsewhere. There was no evidence of platelet dysfunction at this stage. Cyclosporin A therapy was stopped, prednisone 100 mg/day was begun and continued for 14 days. Two weeks after the patient started treatment with prednisone his visual acuity LE was again 0·5, RE unchanged at 1·2. The Amsler grid revealed a definite scotoma, which regressed over the next two weeks. On 23 August 1982 the visual acuity was RE 1·0, LE 0·9.

Follow-up. On 25 August the patient suffered a further relapse and died on 2 November 1982.

CASE 3

A male, born on 30 April 1962.

Primary disease. Acute lymphatic leukaemia, Calla positive, was diagnosed in October 1981. Riehm's induction therapy was started with vincristine, prednisone, doxorubicin, cyclophosphamide, L-asparaginase, methotrexate, and cytarabine. In December 1981 irradiation of the skull was performed with 2000 rads and methotrexate was given intrathecally four times. After treatment with cyclophosphamide 60 mg/kg twice, whole body irradiation with 1000 rads and bone marrow transplantation were performed on 17 September 1981. To prevent graft-versus-host disease cyclosporin A was given 20 mg/kg body weight the day before transplantation, then 10 mg/kg for four days starting on the day of transplantation, then 5 mg/kg for 14 days, 700 mg/day orally.

Eye disease. An eye examination 11 days before bone marrow transplantation showed normal findings. The visual acuity was RE 1·0, LE 1·0 unaided. On 9 December the patient noted visual disturbance and examination revealed a visual acuity of RE 0·4, LE 0·1. Large cotton wool spots and haemorrhages were seen in the fundus of both eyes. One day later both eyes showed multiple cotton wool spots, small haemorrhages, and a Cellophane maculopathy, while in the LE the retina above the papillomacular bundle was oedematous and swollen, giving the appearance of a branch arterial occlusion. In the macula a small serous detachment had appeared.

Visual field examination on 13 January showed a field defect corresponding to this lesion. There was no evidence of platelet dysfunction at this stage.

Follow-up. Cyclosporin A was stopped and prednisone 100 mg/day was given. After 14 days the dosage was reduced. The visual acuity was RE 0·8, LE 0·8. Clinically the patient was well and the bone marrow showed a full remission. Later he developed bronchopneumonia and fibrosing alveolitis (proliferative stage) and died on 10 February 1983. The necropsy showed no signs of a relapse of the acute leukaemia and no obstructive disease of the vessels in the kidney.

Eye at necropsy. A few fine cotton wool spots were visible in the parapapillary region of the right globe. Histology revealed the presence of cytoid bodies in both eyes (Fig. 3), thus confirming unequivocally the clinical diagnosis of cotton wool spots. Step-serial sections did not show any abnormality of the blood vessels supplying the areas of retina containing cotton wool spots, nor was there any evidence of retinal inflammation or infection.

Discussion

The cotton wool spots seen in our patients may be regarded as an expression of small vessel disease, the site of obstruction being at small arterioles, precapillaries, and/or in the capillary bed.

This clinical picture of bilateral cotton wool spots and retinal haemorrhages must be distinguished from the fundus appearance of partial central retinal artery occlusion.[1] The latter condition, which affected only one eye in each of the seven patients described,[1] is characterised by multiple peripapillary cotton wool spots and mild ischaemic swelling of the inner retina but almost complete absence of retinal haemorrhages. Furthermore all patients were suffering from either temporal arteritis, severe hypertension, or embolism.

The multifocal ischaemia of the retina which we describe here could have been caused by any one of a

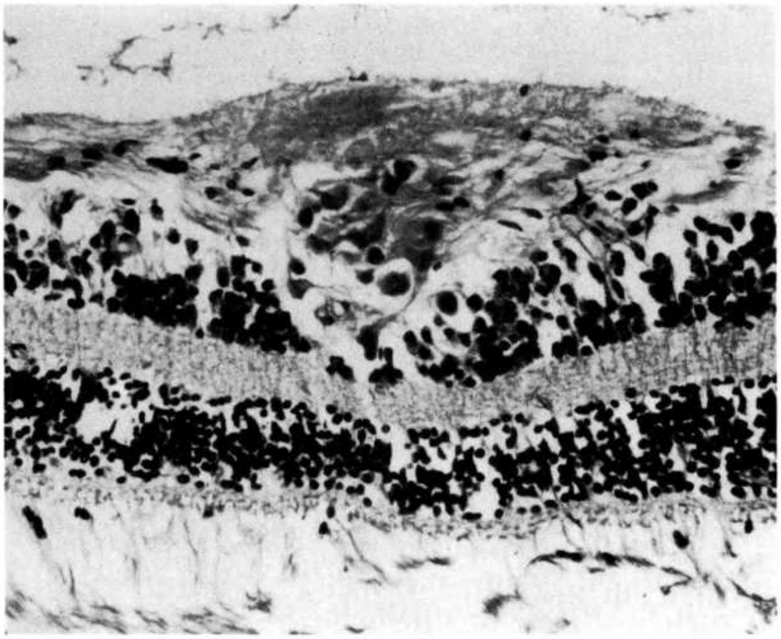

Fig. 3 *Case 3: Typical histological appearance of a cotton wool spot: swelling of the nerve fibre layer and formation of cytoid bodies. (Haematoxylin and eosin, ×220).*

large number of conditions, including iatrogenic factors, infections, immunological or haematological disorders, or vascular disease. However, the most probable causes are acquired immunodeficiency, radiation combined with intrathecal methotrexate, or the administration of cyclosporin A. Viral infections such as cytomegalovirus or herpes simplex, graft-versus-host disease, anaemia, hypertension, and platelet deposition represent less likely causes.

If disseminated retinal ischaemia severe enough to produce visual loss, as in our patients, was caused solely by the immunosuppressives commonly employed in bone marrow transplantation, one would have expected other investigators to have reported this complication, since around 1000 marrow transplants have now been performed. Clearly we must seek other causes, such as radiation and/or cyclosporin A. It is possible that irradiation of the skull with subsequent irradiation of the whole body and the intrathecal administration of methotrexate may predispose to retinal vascular damage. The eye disease would then have its counterpart in the brain: that is, multifocal leucoencephalopathy, which, in contrast to the eye disease, is a known complication in patients given the pretransplantation treatment employed here. The sensory Jacksonian-type epilepsy in our first patient provides some support for this view, although the ocular vessels at this stage no longer showed any evidence of vascular obstruction either in the arterioles, capillaries, or veins. Nevertheless, in none of our three patients does the retinal disease resemble the classical picture of radiation retinopathy, which in addition to cotton wool spots shows sheathing and obliteration of vessels, microaneurysms, neovascularisation, and hard exudates.[2] Furthermore, radiation retinopathy is usually progressive and does not respond to therapy.

The question whether cyclosporin A was directly or indirectly responsible for the retinal changes seen in our three patients must be seriously considered for two reasons. Firstly, although visual symptoms did not occur until some 6–16 months after the diagnosis of leukaemia and irradiation of the skull, the interval between whole body irradiation, bone marrow transplantation, and administration of cyclosporin A and the onset of visual symptoms was only 2–3½ months (Table 1.) Secondly, the most important action of cyclosporin A is suppression of T-helper lymphocytes,[3 4] thus producing a situation very similar to that seen in patients with the immunodeficiency syndrome,[5 6] so long as the picture is not complicated by retinal infection, usually due to cytomegalovirus or *Pneumocystis carinii*. Pepose *et al.*[7] stressed that microvascular and infectious diseases of the retina must not be confused with each other. This is clinically important, because retinal changes due to microvascular disease may respond to steroid therapy, whereas if an infection is also present steroids may lead to disaster, at least if given on their own. In one of our three cases we could demonstrate the presence of typical cotton wool spots histologically, with no evidence of an infectious disease.

But patients with collagen diseases such as lupus erythematosus, dermatomyositis, and scleroderma may also present a similar clinical picture. In dermatomyositis the number of cotton wool spots often exceeds what would be expected from the level of arterial hypertension seen in these patients. All these conditions are autoimmune diseases in which antinuclear antibodies are found and in which the T-helper cells may be suppressed as by cyclosporin A.

Cyclosporin A does not suppress secondary responses. It has no cytotoxic effect and does not lower resistance to bacterial or fungal infections.[3 4] It is most effective in the treatment of graft-versus-host disease, being literally life-saving for many patients, so that extreme caution is indicated before cyclosporin A is implicated as the cause of the retinopathy described here.

It is interesting that we could not find similar retinal changes in 14 renal transplant patients who had received cyclosporin A for 12 months (Oechslin A, Thiel G, Gloor B, personal observations to be published) even though one might expect such changes in patients with kidney disease. On the other hand one of the authors together with Mihatsch (Daicker B, Mihatsch MJ, unpublished observations) has recently found histologically ischaemic optic neuropathies with atrophy of the inner retinal layers in young, healthy rats treated with cyclosporin A. These findings suggest a direct effect of cyclosporin A on small vessels of the retina and/or optic nerve.

Table 1 *Time intervals between ischaemic retinopathy (cotton wool spots) and various therapies*

	Case 1	*Case 2*	*Case 3*
Diagnosis of leukaemia	9 months	16 months	14 months
Irradiation of the skull	6 months	15 months	12 months
Whole body irradiation, Bone marrow transplantation, Therapy with cyclosporin A	90 days	100 days	53 days

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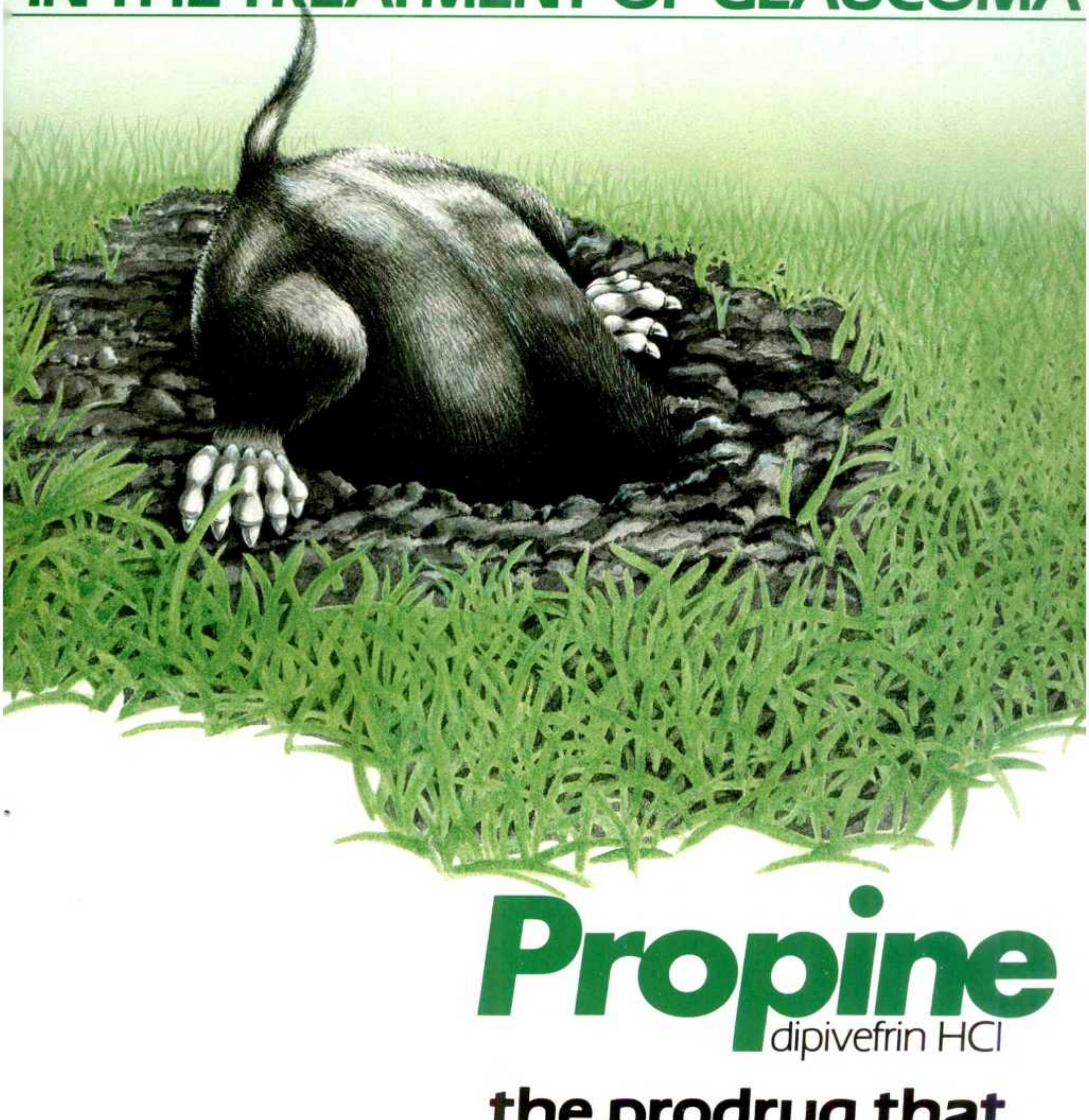

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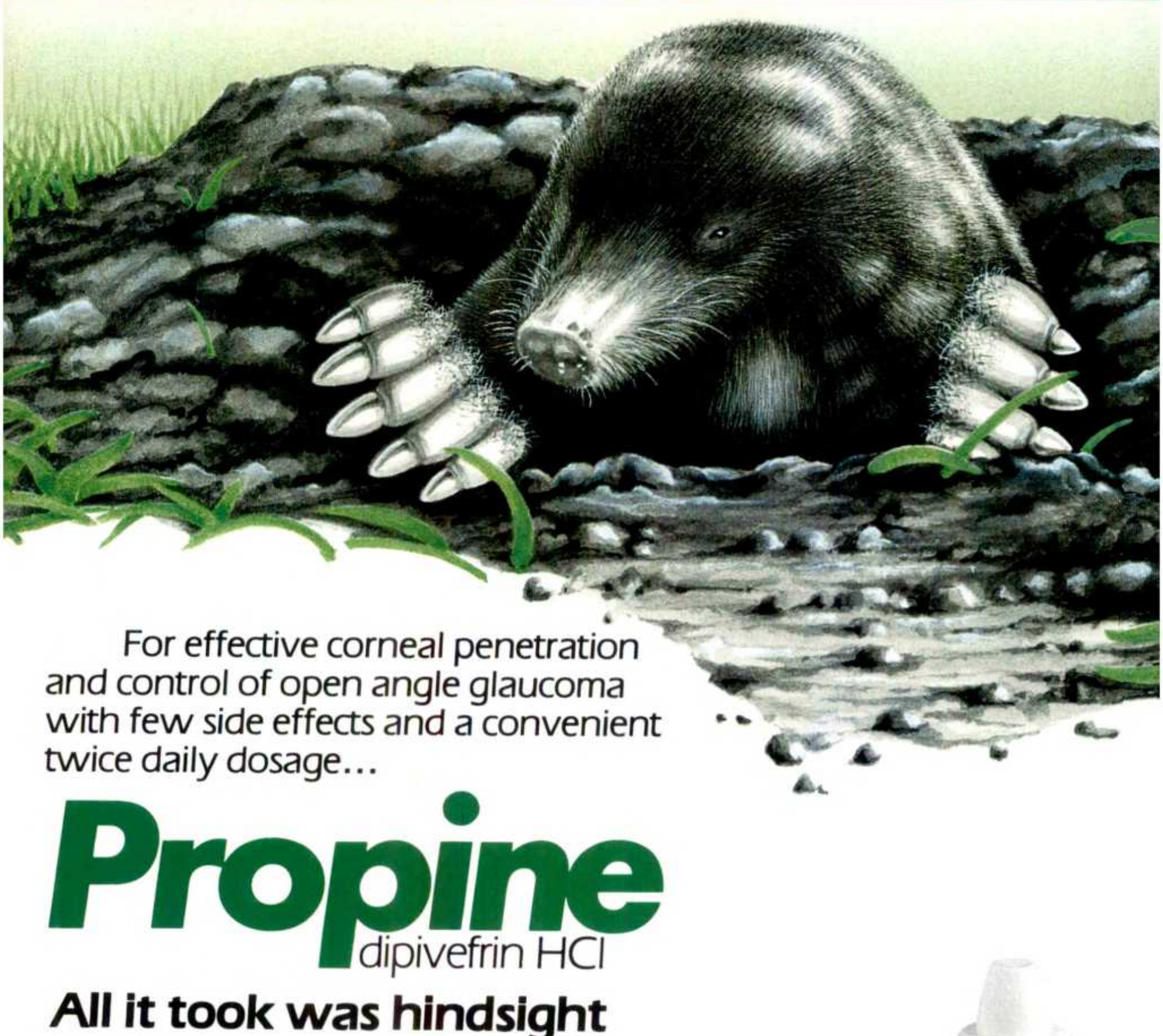

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Unfortunately cyclosporin A was stopped in each of our cases as soon as retinopathy was recognised. We cannot therefore say whether these cases responded to steroids, which were started only when cyclosporin A therapy was stopped. However, it is important to note that the disease process in the retina was reversible. The lack of inflammation in the anterior segment and the complete absence of cells in the vitreous virtually exclude most viral infections. No foci of retinal necrosis, characteristic of cytomegalovirus infection, were seen, neither did the typical pale chorioretinal scars develop subsequently.

The most important ocular complication of graft-versus-host disease affects the anterior segment,[8-10] where a condition resembling Sjögren's disease was first described by Gratwohl *et al.*[11] None of our patients complained of dry eyes. Retinal changes suggesting microvascular disease have not been described in patients with graft-versus-host disease, and the occurrence of haemorrhages in the retina and vitreous probably reflects pancytopenia.[12 13]

Our patients were not anaemic and suffered neither from extreme arterial hypertension nor from hypotension. In none of the three patients was there any evidence that platelet deposition was occurring elsewhere in the body during the period over which the cotton wool spots developed. Nor were any signs of a coagulopathy detected suggesting that platelet dysfunction was not responsible for the retinal changes observed.

In conclusion, the cause of the multifocal retinal ischaemic disease in our three patients remains obscure. It is clearly desirable that all patients submitted to bone marrow transplantation should be examined by an ophthalmologist whether or not they are receiving cyclosporin A. A careful study of renal transplant patients should also be undertaken in an attempt to elucidate any connection between cyclosporin A and the development of retinopathy.

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References

1 Oji EO, McLeod D. Partial central retinal artery occlusion. *Trans Ophthalmol Soc UK* 1978; **98:** 156–9.
2 Brown GC, Shields JA, Sanborn G, Augsburger JJ, Savino PJ, Schatz NJ. Radiation retinopathy. *Ophthalmology* 1982; **89:** 1494–501.
3 Borel JF. *Cyclosporin-A. Pharmacology*. Basle: Sandoz, 1982.
4 Morris PJ. Cyclosporin-A. *Transplantation* 1981; **32:** 349–54.
5 Holland GN, Gottlieb MS, Yee RD, Schanker HM, Pettit TH. Ocular disorders associated with a new severe acquired cellular immunodeficiency syndrome. *Am J Ophthal* 1982; **93:** 393–402.
6 Newmann NM, Mandel MR, Gullet J, Fijikawa L. Clinical and histological findings in opportunistic ocular infections. *Arch Ophthalmol* 1983; **101:** 396–401.
7 Pepose JS, Nestor MS, Holland GN, Cochran AJ, Foos RY. An analysis of retinal cotton wool spots and cytomegalovirus retinitis in the acquired immunodeficiency syndrome. *Am J Ophthalmol* 1983; **95:** 118–9.
8 Jack MK, Jack GM, Sale GE, Shulman KM, Sullivan KM. Ocular manifestations of graft-vs-host disease. *Arch Ophthalmol* 1983; **101:** 1080–4.
9 Kincaid MC, Green WR. Ocular and orbital involvement in leukemia. *Surv Ophthalmol* 1983; **27:** 211–32.
10 Franklin RM, Kenyon KR, Tutschka PJ, Saral R, Green WR, Santons GW. Ocular manifestations of graft-vs-host disease. *Ophthalmology* 1983; **90:** 4–13.
11 Gratwohl AA, Moutsopoulos HM, Chused TM, *et al.* Sjögrentype syndrome after allogeneic bone marrow transplantation. *Ann Intern Med* 1977; **87:** 703–6.
12 Hirst LW, Jabs DA, Tutschka PJ, Green WR, Santons GW. The eye in bone marrow transplantation. *Arch Ophthalmol* 1983; **101:** 580–4.
13 Jabs DA, Hirst LW, Green WR, Tutschka PJ, Santons GW, Beschorner WE. The eye in bone marrow transplantation. *Arch Ophthalmol* 1983; **101:** 585–90.

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A clinical, psychophysical, and electroretinographic survey of patients with autosomal dominant retinitis pigmentosa

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SUMMARY We have surveyed 104 patients (44 families) with autosomal dominant retinitis pigmentosa. The range of the survey includes clinical history, ocular examination, documentation of genetic history, Goldmann kinetic perimetry with IV/4 and I/4 white targets, two-colour static perimetry, and scotopic and photopic electroretinography. Comparison of interfamilial and intrafamilial patterns in the static perimetry data strongly suggests there may be at least two genetic subgroups within the disease characterised by the pattern of loss of *rod* function: in subgroup D (13 patients, 4 families) this is diffuse and severe, while in subgroup R (28 patients, 13 families) it is regional. In both D and R loss of *cone* function is regional, and in R it coincides with loss of rod function. In D patients the rod electroretinogram is absent; in all but two R cases it is present and usually substantial. All D patients were aware of night blindness before the age of 10, but most R patients not until after the age of 20. Many of the patients could not be classified because their disease was so advanced. The effect of disease duration on visual acuity and visual field area is described for all patients.

Retinitis pigmentosa (RP) is a term used to denote a group of disparate, genetically determined disorders characterised clinically by nyctalopia, progressive loss of visual field, a characteristic appearance of the fundus, and preservation of good visual acuity until late in the disease process. So far a clearly defined subdivision has not been devised except on genetic grounds. A better subclassification would help in advising the patient and is required if research into pathogenesis or treatment of these disorders is to be successful.

The mode of inheritance of RP may be autosomal recessive (AR), autosomal dominant (AD), or X-linked (X-L). There is, however, evidence of heterogeneity within the genetic subgroups. Krill[1] suggested that division of AR disease into those with early onset and those with late onset may be helpful. Berson *et al.*[2] suggested that AD RP may be divided into two groups on the basis of gene penetrance (namely, full and reduced), and stated that the temporal characteristics of the electroretinogram differ between the two groups. Further subdivision of both simplex and AD RP has been suggested by Massof and Finkelstein[3] based on different relationships between rod and cone sensitivity as determined by two-colour static perimetry on the dark adapted eye. These authors[4] have developed their classification for AD RP and have also noted differences in the age of onset of night blindness between the two subtypes they propose. Other authors have proposed subgroups on the basis of electroretinographic data.[5 6]

Heterogeneity within a genetic group may be explained by the effects of different genes, which, if proved, would render subdivision helpful to research in that each subgroup would represent a pure sample of one disease. However, subdivision would be unhelpful if the different characteristics were due to observation of the same disorder at different stages of evolution or different phenotypic expression of the same genetic abnormality.

In the present study our main objective was to determine whether we could define reliable criteria

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by which AD RP could be subdivided. We have therefore surveyed a large number of patients with this inheritance pattern. Where possible, large family units were examined. Our approach was to attempt to characterise the disease within a family and then to compare interfamilial and intrafamilial variation. We used the techniques of electrophysiology, static perimetry, Goldmann kinetic perimetry, and clinical examination.

Patients and methods

PATIENTS

Affected members from families with autosomal dominant retinitis pigmentosa were invited to take part in this study; 104 patients were examined, ranging in age from 11 to 77 years. The age and sex distribution of the patients is shown in Table 1. As many affected family members as possible were recruited, and the genetic histories were verified with the patients. AD RP can be diagnosed with confidence where there is transmission through three generations, equal male and female involvement, and male to male inheritance. The diagnosis was, however, assumed where there were two or more identified affected generations, with equal severity of disease in males and females, but in the absence of male to male inheritance. Table 2 gives genetic details of the families.

Among patients with signs of RP and AD inheritance we have seen those whose fundus changes are restricted to a small area of retina, usually in the inferior, nasal quadrant. Though the functional changes may be more widespread, they are usually minimal in the area of retina which has a normal appearance. A comparison of family members of various ages suggests that there is no marked progress of the disease outside the area of retinal change. Such cases, commonly described as sector RP, are considered to be a distinct form of disease and have not been included in the present survey.

Table 1 *Age and sex distribution of the patients studied*

Age groups (years)	*Male*	*Female*
0–9	0	0
10–19	5	9
20–29	11	10
30–39	6	20
40–49	7	13
50–59	4	9
60–69	5	4
70–79	1	0
Total	39	65

CLINICAL EXAMINATION

A clinical history was taken with specific questions being asked about (1) the age of onset of night blindness, (2) the age of onset of loss of visual field, and (3) the age of onset of any loss of visual acuity which could not be corrected with glasses. The visual acuity of each eye was measured after correction of any refractive error. Slit-lamp examination and examination of the fundus by indirect ophthalmoscopy and Hruby lens were performed routinely. A note was made of the presence or absence of lens opacities and their type when present, and the presence or absence of vitreous cells. The following attributes of the fundus were recorded: disc colour, retinal vessel changes, pigment changes at the level of the pigment epithelium and neurosensory retina, the distribution of changes, and the presence or absence of retinal oedema. Colour photography and fluorescein angiography were performed on most of the patients.

SPECIAL EXAMINATIONS

Visual fields were recorded with a calibrated Goldmann perimeter using the IV/4 and I/4 white targets. Upper field (above the horizontal meridian) and lower field (below the horizontal meridian) areas were measured by placing transparent graph paper over the Goldmann charts and measuring in cm^2 the areas enclosed by the respective contours.

All patients were examined with a two-colour, automated, static perimeter which consists of a rotatable Lister arm in which the targets have been replaced by two light emitting diodes (LEDs) suitably filtered to emit green light of dominant wavelength 530 nm and red light of dominant wavelength

Table 2 *Genetic details of patients*

	Male to male			*No male to male*		
	2 Gen	*3 Gen*	*>3 Gen*	*2 Gen*	*3 Gen*	*>3 Gen*
Families	3	9	6	8	11(1)	7(1)
Males	3	12	10	6	8	0
Females	1	8	14	17	11(1)	14(2)

Numbers in brackets refer to families with incomplete penetrance or to individuals from such families. Gen=generation.

660 nm. The light intensity can be varied in steps of 0·1 log unit over a range of 5 log units. The maximum luminance of the filtered green LED is 0·9 log cd m^{-2} and that of the filtered red is 2·2 log cd m^{-2}. The perimeter is linked to a computer and visual thresholds can be measured at various locations in the visual field, as determined by a preset computer program; the results are stored immediately. Thresholds are usually expressed as the logarithm of the ratio of the patient's reading to the mean normal value based on data collected from a minimum of 15 observers.[7]

The use of two colours, one green and one red, permits an assessment of the relative sensitivity of the rod and cone mechanisms in a particular region of the retina. Disturbance of rod function is identified by a threshold elevation for the green test light and of cone function by a threshold elevation for the red test light. The difference between the logarithms of these two values (subsequently referred to as the G-R index) is a measure of the degree to which rod function is more selectively disturbed than cone function. To a first approximation, when the difference is near zero, the disturbance is affecting cone vision to the same or greater extent than rod vision. When the difference assumes a significant positive value, then rod vision is being disturbed to a greater extent. The interpretation of the threshold data is discussed in more detail by Ernst *et al.*[7]

The technique used for electroretinography is described by Arden *et al.*[8] Gold foil electrodes were used and electroretinograms (ERGs) evoked by a variety of ganzfeld stimuli. Of particular interest were responses obtained from blue flashes, which in normal observers tended to produce a saturated rod b wave (run 12, Arden *et al.*[8]) and red flashes which gave an ERG with a distinct cone b wave (run 18).

Results

STATIC PERIMETRY

For static perimetry the majority of patients were tested at 30 to 40 locations on four meridians (0°, 60°, 180°, 315°) in the right eye (see Ernst *et al.*[7]). To describe the main features of a patient's field losses we have found it sufficient to display results taken from the horizontal meridians (0° and 180°).

Fig. 1 (upper) shows a patient's thresholds (crosses) for the green target on the horizontal meridian, together with mean normal values for the same locations (asterisks). These normal means are subtracted from the patient's data to give log relative thresholds (Fig. 1, lower). To reduce the data further we have divided the meridians into five zones as shown in Fig. 1 (lower); data from the 20°–40° and 50°–70° zones have been averaged. The result from each zone is indicated by a particular symbol—for example, a square represents a value for a 10° eccentricity in the temporal field. Data obtained with the red target have been processed in a similar manner.

To permit comparison between patients we have rearranged the data from any one patient (e.g., Fig. 1, lower) so that log relative thresholds from the five zones appear on one vertical axis with a solid line linking the extreme values; data from other patients can then be presented alongside (Fig. 2A).

Illustrative data from four families are presented in Figs. 2A, B, C. There was a close similarity between the pattern of results shown by individuals in the same family. These four families also displayed two contrasting patterns. In families 30 and 225 the log relative thresholds for green were high throughout

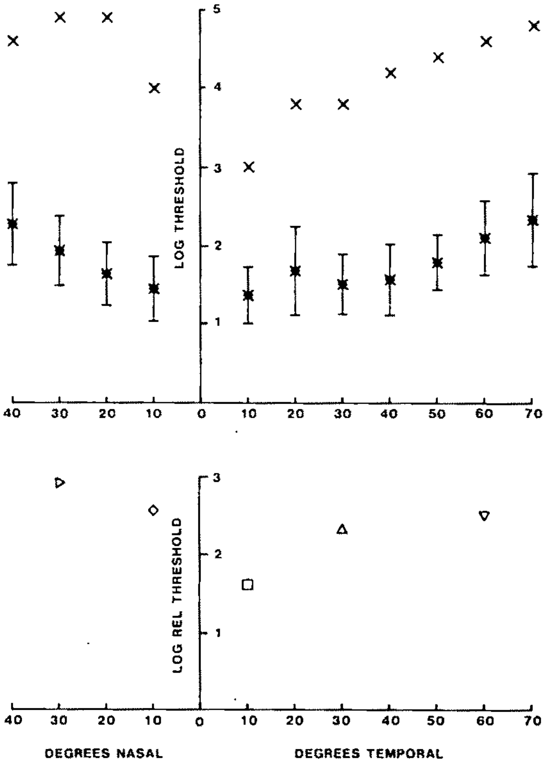


Fig. 1 Upper: *Log threshold for the green target on the horizontal meridian. Crosses=data from patient 30/74. Asterisks=normal means. Bars=standard deviations.* Lower: *Patient's data from Fig. 1* (upper) *transformed to give log threshold values relative to normal in five zones: 20–40° nasal (right-pointing triangle); 10° nasal (diamond); 10° temporal (square); 20–40° temporal (upward-pointing triangle); and 50–70° temporal (downward-pointing triangle). Values in the 20–40° zones and the 50–70° zone averaged.*

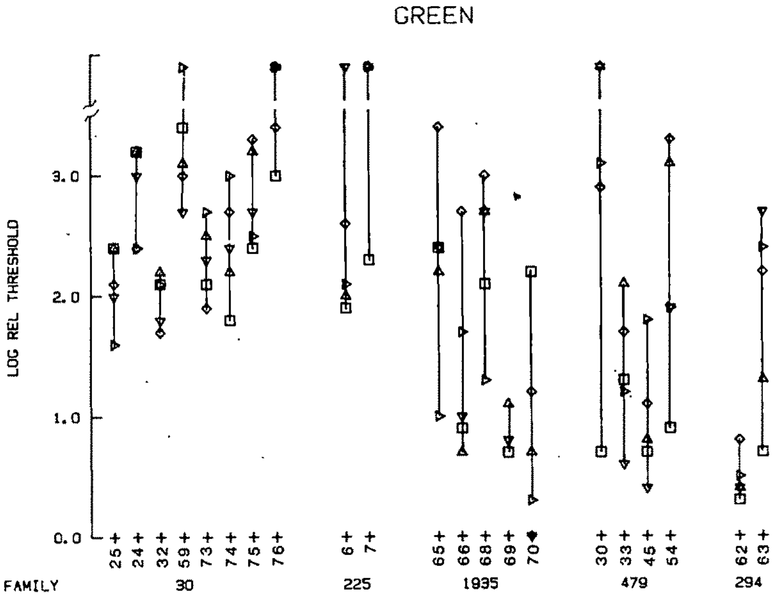


Fig. 2A *Log relative thresholds for the green target in the five zones placed on a vertical axis. Axis broken to accommodate off-scale readings. Symbols as for Fig. 1 (lower). Lines link extreme values. Data from four families, 30, 225, 1935, and 479, are presented and individual members are identified by separate numbers arranged horizontally.*

the visual field, and thresholds at no point lay within 1·5 log units of normal (Fig. 2A). Families 1935 and 479, however, showed a wide range of readings for green extending from near normal to 'off scale' for different locations. Thus in families 30 and 225 there was severe and widespread loss of rod function, whereas in families 1935 and 479 there were some zones with severe rod disturbance, but there was at least one zone with near normal rod function.

The four families demonstrated a spread of readings for the red target from those indicating near normal cone function to those indicating a cone disturbance (Fig. 2B). In general, for families 30 and 225 the red threshold elevations lay below the green ones (Fig. 2B), whereas in families 1935 and 479 red and green threshold elevations overlapped, with the loss for each being similar (Fig. 2B—the solid line represents the range of the green readings). This is more clearly emphasised in Fig. 2C, where predominantly high G-R index values were obtained for

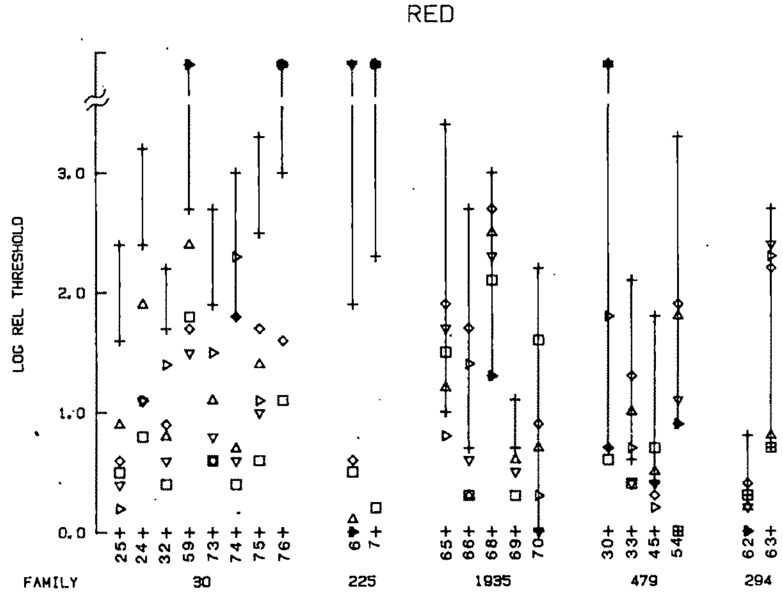


Fig. 2B *Log relative thresholds for the red target in families 30, 225, 1935, and 479. The lines are those of Fig. 2A and show the spread of readings with the green target. The symbols show the readings with the red target and have the meanings defined in Fig. 1 (lower).*

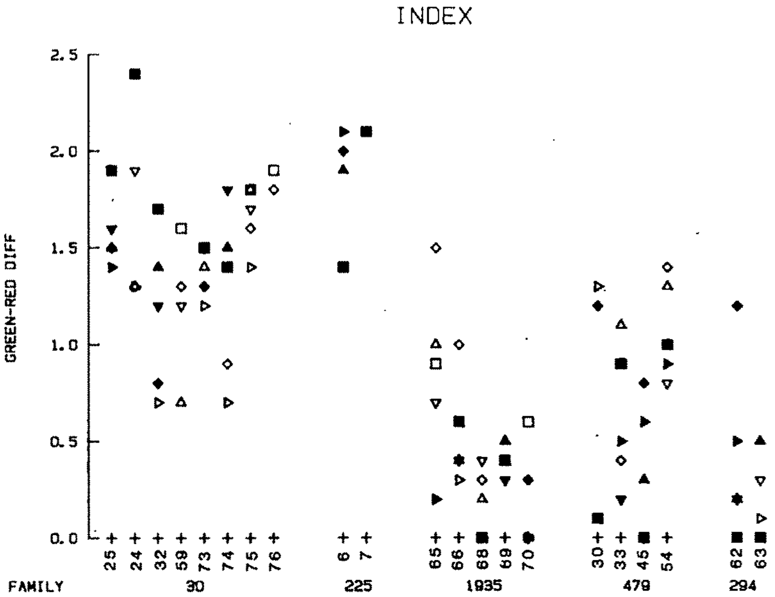


Fig. 2C *G-R index for families 30, 225, 1935, and 479. Filled symbols represent those index values associated with a threshold elevation for the red target of <1 log unit.*

families 30 and 225, indicating a much greater disturbance of rod function than cone function, and generally lower index values were present in families 479 and 1935, indicating that rod and cone losses were similar within a given area. However, there was an overlap of index values between the two sets of families, and low values in family 30 indicated that, though rod thresholds might be highly elevated, rod function was present. Absence of rod involvement in the detection of the green target requires an index value of about 2.[7] A distinguishing feature is that, where cone function was near normal (indicated by the filled symbols), the index reached values of 1·5 or more in some zones for families 30 and 225 but was always less for families 479 and 1935.

We have derived criteria for classifying patients

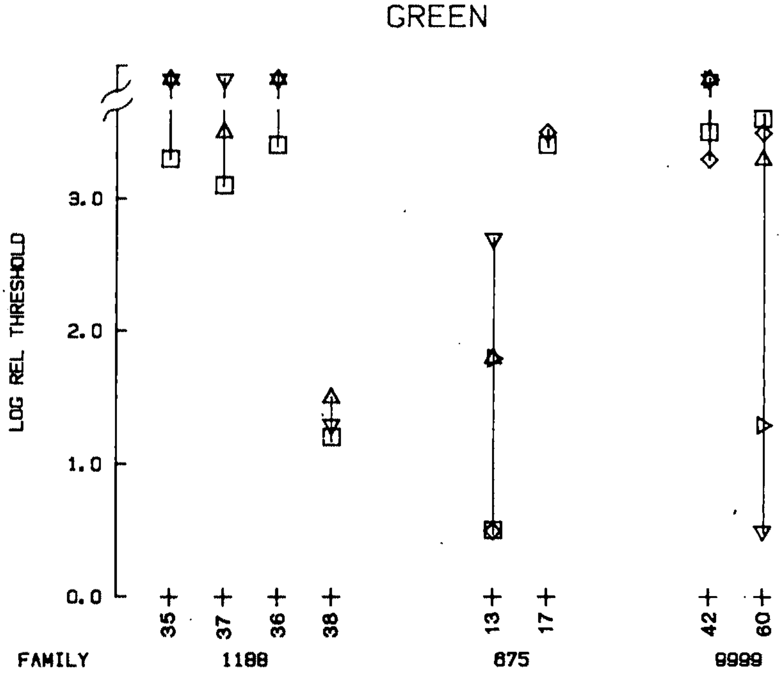


Fig. 3A *Log relative thresholds for the green target in families 1188, 675, and 9999. See legend to Fig. 2A.*

from the features seen in Fig. 2. The criteria for a diffuse and selective pattern of rod loss, pattern D, are: (1) in all zones threshold elevations for the green target must be greater than 1·5 log units; (2) in at least one zone the elevation for the red target must be less than 1 log unit, and this must be accompanied by an index value of greater than 1·5. The diffuse description applies only to loss of rod function; loss of cone function may be regional, as in family 225. The criteria for a regional loss of both rod and cone function, pattern R, are: (1) in at least one zone threshold elevations for both red and green targets must be less than 1 log unit; (2) in at least one zone threshold elevations for the two targets must be greater than 0·5 log unit. That these criteria are somewhat arbitrary can be seen in family 30 (Fig. 2B): two patients, 30/59 and 30/76, did not show any zone where threshold elevations for the red target were less than 1 log unit, even though the general pattern of their data was in line with other members of the family. Similarly, patient 1935/68 failed to conform to the strict pattern R criteria because in no zone did the threshold elevation for both targets fall below 1 log unit. In these three cases from large families, and one other from a family of 8, we have relaxed the criteria and classified the individuals according to the family pattern. However, where such family information has not been available, we have not classified any patients who did not fulfil the criteria for either pattern. Thirteen individuals from four families showed pattern D behaviour, 28 from 13 families pattern R; the remaining 63 were unclassifiable and are referred to as U patients. Nineteen of the U patients had Goldmann fields of 5° or less for the I/4 target and gave 'off scale' threshold readings for both static perimetry targets outside a 5° eccentricity.

Figs. 3A, B, C show results from three families illustrating some of the problems in classification. Although patients 1188/35, 1188/36, and 1188/37 had severe and diffuse loss of rod function, this was not the case with patient 1188/38, who showed a mild rod loss accompanied by near normal cone function at the tested locations. No member of the family fulfilled the criteria for either pattern D or R, and they were all placed in the U category.

In families 675 and 9999 patients 675/17 and 9999/42 showed severe and diffuse loss of rod function with better preservation of cone function (Fig. 3), and it might be thought they were similar to pattern D patients. However, the other family member in each case clearly conformed to pattern R criteria. It is plausible to suggest that the regional pattern is lost as disease progresses; both patients 675/17 and 9999/42 had limited fields, and cone function, where preserved, was severely disturbed. In the absence of further information they have both been placed in the U category. This example emphasises the importance

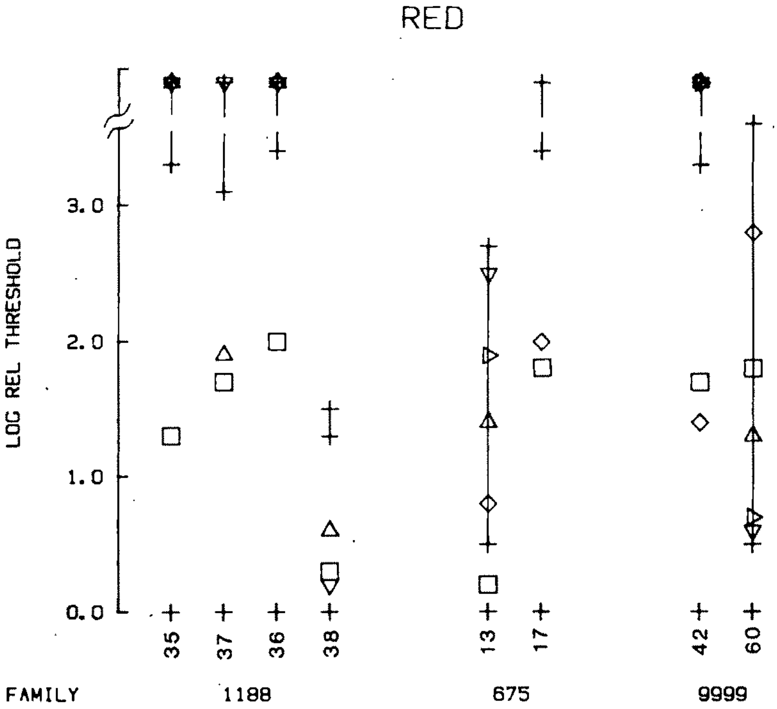


Fig. 3B *Log relative thresholds for the red target in families 1188, 675, and 9999. See legend to Fig. 2B.*

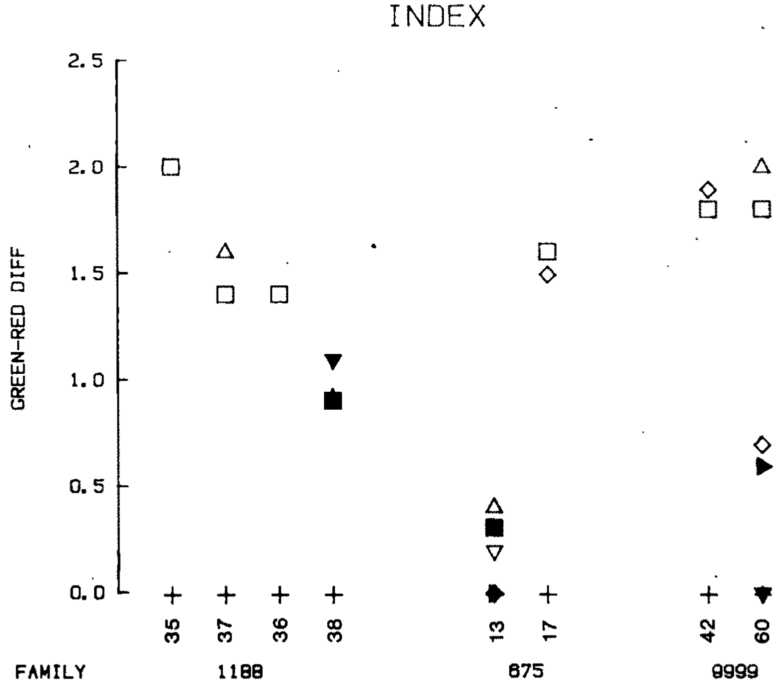


Fig. 3C *G-R index for families 1188, 675, and 9999. See legend to Fig. 2C.*

for classification of having a region where cone function is nearly normal: if rod function is poor in the same region, this indicates pattern D, if nearly normal, pattern R.

The G-R index in a patient with severe losses may be a poor guide to the pattern initially present. In pattern D, if cone losses proceed more rapidly than rod losses in a region, and if rod function can still be detected with the green target, the value of the index will drop. This may be what has happened in some members of family 30 (Fig. 2C). Conversely, in pattern R, if rod function is lost more rapidly than cone function in an affected zone, a high index value will result and this may be the explanation of the high values seen in patients 675/17 and 9999/42, assuming that they started out with pattern R.

ELECTRORETINOGRAPHY

Electroretinography was carried out on 77 individuals and responses greater than 5 μV were obtained from 57. No rod ERG, either a or b wave, as determined by spectral sensitivity and waveform criteria, could be detected in any pattern D patient, whereas rod ERGs were recorded from all but two of the pattern R individuals. Some of the latter produced ERGs with amplitudes in the normal range—that is, within 2 standard deviations of the mean normal value for a particular stimulus. According to the classification adopted by Arden *et al.*[6] all pattern D patients belong to the A subgroup and all but two of the pattern R patients to the B subgroup (the two exceptions belong to the A2 subdivision—that is, no rod ERG but rod psychophysics). However, subgroups A and B also include U patients who have not been classified by static perimetry.

Fig. 4 summarises some of the ERG data. It consists of histograms showing how many of the patients in each of the subgroups D, R, and U produced a b wave in a given amplitude or latency range for a particular stimulus. Results are shown for two stimuli: (1) a blue flash sufficiently bright to elicit a saturated rod response in normal observers but not bright enough to yield a significant contribution from the cone system; (2) a red flash which in normal observers separates out cone (a1 and b1 waves) and rod components (a2 and b2 waves) and produces saturated cone ones; the data shown refer to the cone b1 waves. The range label N refers to responses falling within normal limits (see above) and the labels A^+, A^{++}, A^{+++} refer to increasing degrees of abnormality (see legend to Fig. 4). The ND category refers to the cases where measurements were not done.

The amplitude information (Fig. 4, left side) shows that, for the blue flash, all D patients fell into the A^{+++} and A^{++} category (the small responses here being due to the cone system), while all but three of the R patients fell into the A^+ and N categories. On the other hand for the red flash the difference

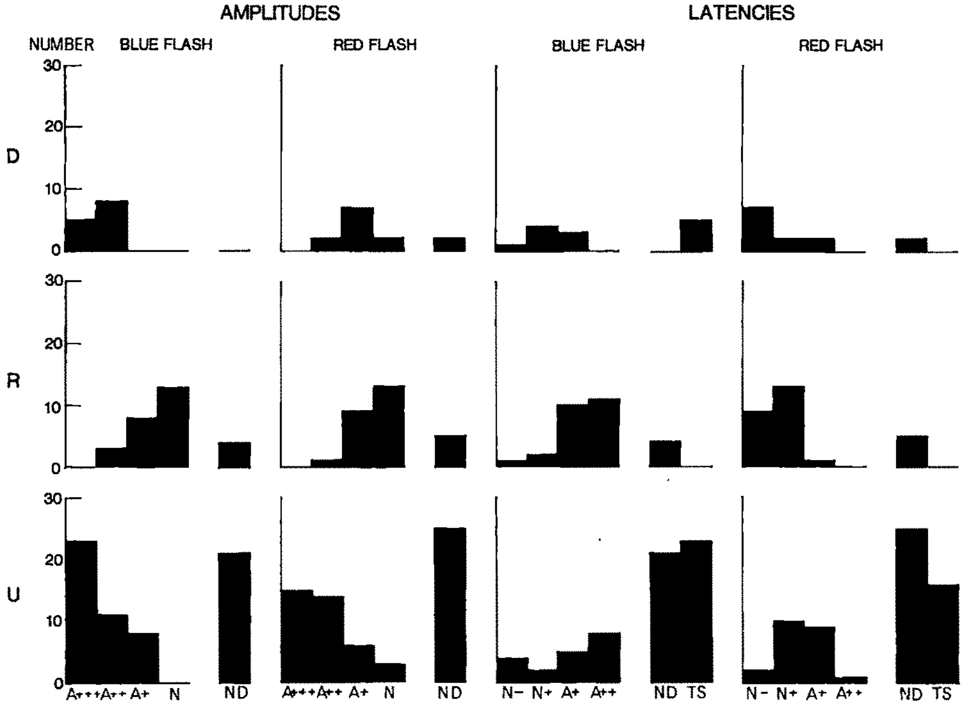


Fig. 4 *Distribution of ERG amplitudes and latencies for the AD RP subgroups. D: subgroup with diffuse rod loss; R: subgroup with regional receptor loss; U: unclassified. Blue flash refers to run 12 of Arden* et al.,[8] *red flash to run 18. 'Red flash' amplitudes and latencies refer to cone b wave. N=within 2 standard deviations of normal mean. A+, A++, etc.=increasingly abnormal. ND=not done. TS=too small to measure. For 'blue flash' amplitudes N=>140 μV; A+=20–140 μV; A++=5–19 μV; A+++=<5 μV; mean normal amplitude=319 μV. For 'red flash' amplitudes N=>59 μV; A+=20–59 μV; A++=5–20 μV; A+++=<5 μV; mean normal amplitude=153 μV. For 'blue flash' latencies N−=<57 ms; N+=57–69 ms; A+=70–79 ms; A++=>79 ms; mean normal latency=57 ms. For 'red flash' latencies N−=<47 ms; N+=47–57 ms; A+=57–69 ms; A++=>69 ms; mean normal latency=47 ms.*

between the groups disappeared: the majority of both D and R patients fell into the A^+ and N categories. This is expected, because assigning an individual to either group requires near normal cone function in some parts of his or her visual field. Likewise the preponderance of U patients in the A^{+++} and A^{++} categories for both blue and red flashes is expected because they have very poor rod and cone function.

As regards the latency distributions (Fig. 4, right side), the blue flash values for the D patients are not informative, since they are derived from cone responses and the norms are for rod b waves. For the R patients most of the values were abnormal. The complete amplitude-intensity functions for these patients show that they responded as if the stimulus intensity had been reduced (see Arden *et al.*[6]). Since latencies are more sensitive to changes in effective intensity over this range, this would explain, at least in part, how amplitudes in the normal range can go hand in hand with abnormal latencies. The high proportion of nearly normal latencies for the red flash responses in both D and R groups again reflected the bias introduced by the classification procedure. Interestingly, in some members of the D group a normal latency for the red flash b1 wave was accompanied by abnormal timing in the responses to very bright white light flickering at 30 Hz (run 31, Arden *et al.*[8]); the reason for the discrepancy is not clear. None of the D or R patients, so far as we are aware, belong to autosomal dominant families with incomplete penetrance. In the case of the U group most of the responses were too small, if they existed at all (TS category), for latency measurement and the few values in the normal range seen for the blue flash resulted from an inappropriate comparison of cone ERGs with rod norms, as in the case of the D patients.

Arden *et al.*[6] have attempted to predict ERG amplitude versus log intensity functions from psychophysical data on the basis of a model with a number of simple assumptions. In the case of data from D

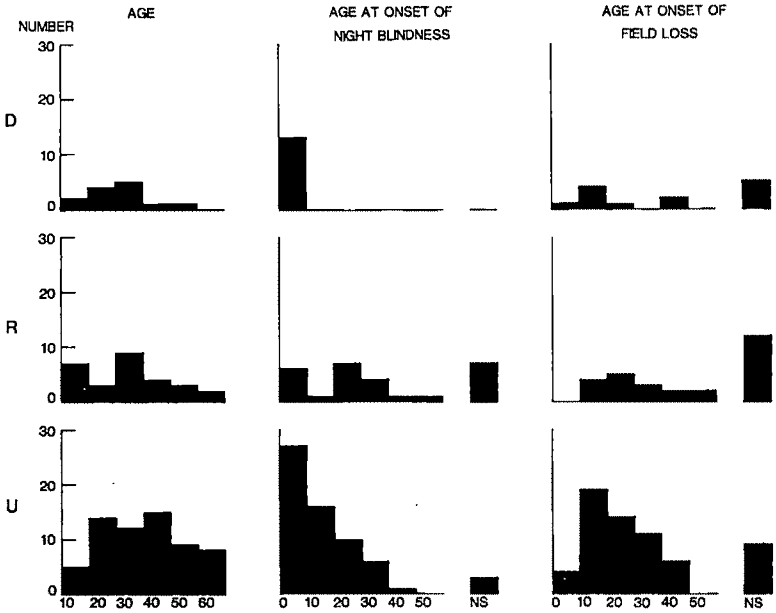


Fig. 5 *Distribution of ages at examination, ages at onset of night blindness, and ages at onset of field loss for the AD RP subgroups.*

patients analysed this way the model successfully accounted for the absence of measurable rod ERGs. In the case of 10 R patients (the data from the remaining 18 were not available) the model gave good fits to the ERG data in four cases, but in six the actual loss in ERG sensitivity as measured by the shift of the amplitude versus log intensity function along the log intensity axis was much smaller than predicted from the psychophysical results. Moreover, the maximum b wave amplitudes were smaller than expected.

SYMPTOMS

Fig. 5 summarises (1) the distribution of ages among patients in the three groups, D, R, and U; (2) the distribution of ages at which they first became aware of problems in the dark; and (3) the distribution of ages at which they first remembered having visual field problems (NS refers to those patients claiming no symptoms). All D patients reported night blindness before the age of 10 and none were asymptomatic. By contrast, the majority of R patients reported problems occurring after the age of 20, or were asymptomatic. Of the seven exceptions, in two cases there was definite reason to doubt the usefulness of the patients' reports, for the functional state of their rods, as judged from the static perimetry and ERG data, was not severely disturbed and not very different from that of other members of their families who all reported late onset. In the other cases, especially in two of them who lacked rod ERGs, functional losses were more consistent with the patients' reports of early onset. In the U group the majority reported early onset.

There is little significant difference between the D and R groups in age of onset of field loss. In the R group there was a tendency for patients to report awareness of field losses and night blindness at the same time. The two events were separated by five years or less in nine of the 13 patients who reported both symptoms. In the D group the separation was less than five years in only two patients, while, in six of the remaining 11 in the group the separation was more than 20 years or else field loss was not reported, even though night blindness had been experienced more than 20 years earlier. The U group showed a distribution skewed to early field losses, which is consistent with the small fields seen in most of them at the time of their examination.

VISUAL ACUITY

Table 3 summarises the distribution of visual acuities among the patient groups. All but two of the D and R patients had acuities better than or equal to 6/12. In

Table 3 *Distribution of visual acuities in the groups of AD RP*

Visual acuity	*Number of D*	*Number of R*	*Number of U*
>6/12	8	24	21
=6/12	4	3	12
<6/12	1	1	28
No information	0	0	2

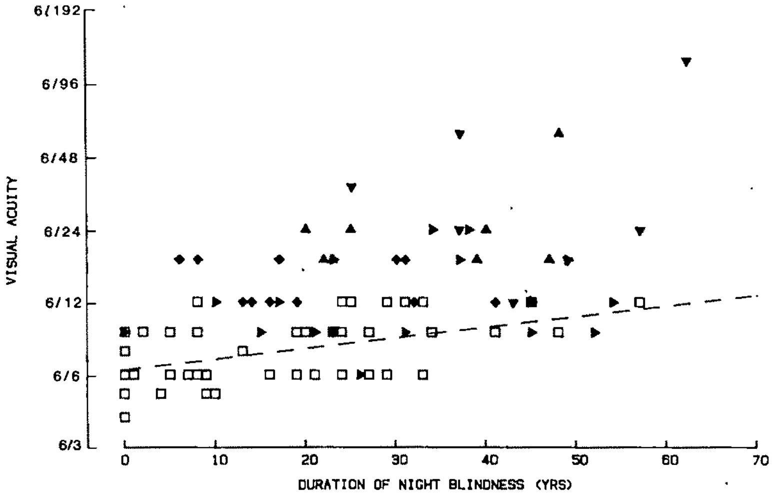


Fig.6 *Log$_2$ visual acuity as a function of duration of night blindness. Line is derived from a stepwise linear regression (Minitab) involving five explanatory variables, var1=duration of night blindness; var2=presence (right-pointing triangles) or absence of lens opacities; var3=presence (diamonds) or absence of macular oedema; var4=presence (upward-pointing triangles) or absence of both lens opacities and macular oedema; var5=presence (downward-pointing triangles) or absence of both lens opacities and macular atrophy; unfilled squares indicate cases with no lens or macular problem. The model used:*

$$\log_2 VA = 0{\cdot}0664 + 0{\cdot}0147 * var1 + 0{\cdot}49 * var2 + 0{\cdot}81 * var3 + 1{\cdot}48 * var4 + 1{\cdot}60 * var5.$$

$R^2 = 68\%$; mean square residual $= (0{\cdot}495)^2$; number of cases=93; degrees of freedom=87.

the U group about 46% had acuities less than 6/12; this probably reflects the selection bias introduced by the method of classification.

Any patient with a visual acuity of less than 6/12 had either macular oedema or macular atrophy, and/or lens opacities. Decreased acuity at an early age or after a short duration of night blindness was due to macular oedema, except in one patient aged 55 years who had age-related cortical lens opacities. All but one of the patients with cataract had posterior subcapsular lens opacities; three also had nuclear sclerosis, and only one had peripheral cortical opacities.

A more detailed analysis of the dependence of visual acuity on disease duration and lens and macular problems was carried out with the help of the statistical package, MINITAB, which treated log$_2$ acuity as a linear function of a series of explanatory variables and performed stepwise regression on the data. The following information was entered for each patient: (1) visual acuity expressed as a log$_2$ ratio; (2) age at time of examination; (3) duration of symptoms of nightblindness; (4) duration of symptoms of field loss; (5) the presence (scored as 1) or absence (scored as 0) of lens opacities; (6) the presence or absence of macular oedema; (7) the presence or absence of macular atrophy. Full data were available on 93 patients. For this analysis no distinction was made between the subgroups. The most economic description of log$_2$ VA was in terms of a linear model with five explanatory variables, namely: (1) night blindness duration; (2) lens opacities without macular problems; (3) macular oedema without lens opacities; (4) macular oedema with lens opacities; (5) macular atrophy with lens opacities. The model states that for every year of night blindness visual acuity is reduced by a factor of 1·01; a score of 1 for one of the other variables leads to a further independent reduction by a factor of 1·40 for a lens opacity, 1·75 for macular oedema, 2·79 for the combination of lens opacity and macular oedema, and 3·03 for a combination of lens opacity and macular atrophy. Fig. 6 shows the visual acuity data on a log$_2$ scale plotted as a function of duration of night blindness, with other factors indicated by various filled symbols. The dashed line is the model's prediction of the effect of the night blindness duration alone and provides a reasonable fit to the unfilled squares, which represent data from patients without macular or lens complications.

An almost equally satisfactory model can be set up by replacing duration of night blindness by duration of field loss symptoms, but substitution of age for either of the duration variables leads to a poorer fit. Since the three variables are correlated (the correlation coefficient between the duration variables is 0·78 and between age and night blindness duration 0·67), only one of them needs to be represented in the model. Thus our data provide no evidence of any effects of age per se which are not accounted for by the duration of the disease or a lens or a macular problem.

GOLDMANN FIELDS

In most patients the area of upper visual field, as measured by the Goldmann field target IV/4, was considerably smaller than the area of the lower field;

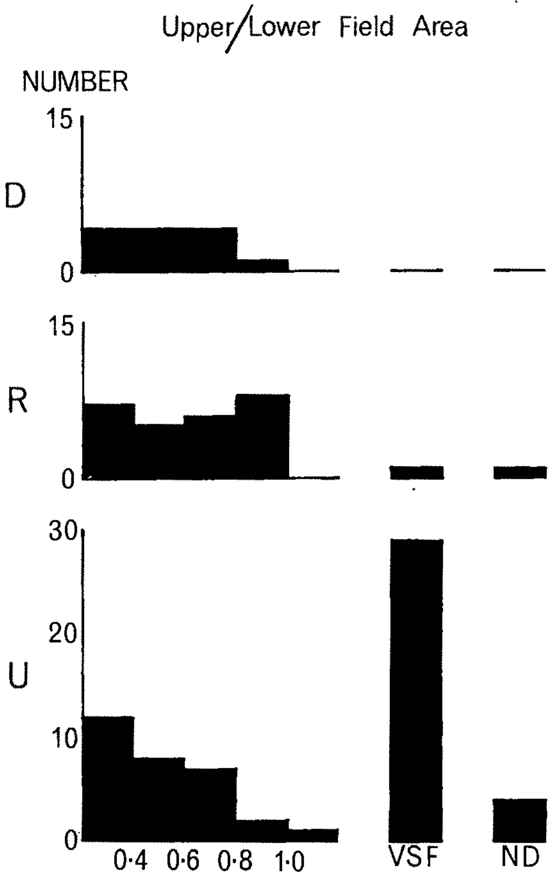


Fig. 7 *Distribution of field area ratios (upper/lower) for the AD RP subgroups. VSF=very small fields. ND=not done.*

the ratio of the two areas was typically smaller than the normal ratio of 0·9. Fig. 7 shows the distribution of ratios for the three patient groups (VSF refers to those patients with very small fields where the ratio is not meaningful and ND to those cases where the fields were not done). Full or partial ring scotomas were seen in all groups but the numbers in each were very small. Qualitatively the appearance of fields was similar for the two eyes in most of the patients.

In general the area of the visual fields was related to the length of time visual field problems had been experienced. Fig. 8 shows $\log_e$ of the field area in cm^2 enclosed by the contour for the IV/4 target, plotted as a function of duration of field loss. The results from the three goups have not been distinguished, since most of the D and R patients have experienced field loss symptoms for less than 10 years.

The combined field area scores together with the information used in the analysis of visual acuity were analysed by a stepwise linear regression procedure. The dependent variable, $\log_e$ field area, can be represented as a linear function of two explanatory variables, namely (1) duration of field loss and (2) the presence of both a lens opacity and macular oedema. If all the data are considered, the model predicts that for every year of noticeable field loss there is a decline in field area by a factor of 1·09 (dashed line of Fig. 8). However, the line is biased by a point obtained from a patient with 59 years of field loss who had an unusually large area from an island of vision surviving in his inferior field. If this point is excluded, the model predicts a decline by a factor of 1·11 per year of field loss (solid line). The presence of an opacity together with macular oedema (indicated by the circled points) independently reduces field area by a

Fig. 8 *$\log_e$ field area as a function of duration of field loss. Lines derived from stepwise linear regression (Minitab) involving two explanatory variables, var1=duration of field loss, var2=presence (circled points) or absence of both lens opacities and macular oedema. The models used:*

(1) all points included (dashed line):

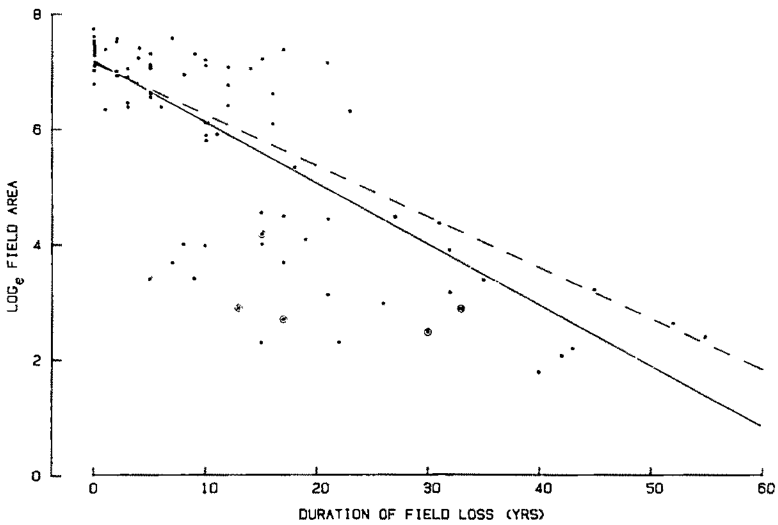
$$\log_e \text{field area}=7{\cdot}14-0{\cdot}0882*\text{var1}-2{\cdot}00*\text{var2}.$$

$R^2=55{\cdot}8\%$, mean square residual $=(1{\cdot}23)^2$; number of cases=90; degrees of freedom=87;

(2) One extreme point excluded—see text (solid line):

$$\log_e \text{field area}=7{\cdot}19-0{\cdot}105*\text{var1}-1{\cdot}83*\text{var2}.$$

$R^2=63{\cdot}3\%$; mean square residual $=(1{\cdot}22)^2$; number of cases=89; degrees of freedom=86.



further factor of 6·23. However, it is clear that the model can give only a very approximate description of the field area data. It should be remembered that the analysis has two major weaknesses—namely, the duration of field loss is a subjective variable, and the analysis is based on a cross-patient comparison of a group which is not likely to be homogeneous.

APPEARANCE OF FUNDUS

Most of the patients had attenuated retinal vessels and pale discs. Early change was seen as a greying of the pigment epithelium. With later migration of pigment into the retina the pigment epithelium assumed an atrophic appearance. The area of maximum involvement was usually, though not exclusively, the mid periphery, with a zone anterior and posterior to this which showed lesser degrees of pigment epithelial change. The area within 10° radius from fixation was usually uninvolved, unless macular oedema or atrophy was present. As might be expected for progressive disease, a sharp cut-off is not seen. The degree of pigment migration into the retina was greater the longer the duration of the disease and the greater the age of the patient. The area of maximum change in the fundus agreed well with the area of field loss measured with the Goldmann IV/4 target. Thus changes in the inferior compared with superior retina were generally more prominent. This might be due to the effect of more illumination on the inferior retina or the result of intrinsic retinal factors. On examination of the fundi no differentiating features could be found between D and R patients.

Discussion

NATURE OF THE SAMPLE

Most previous studies of RP have been carried out on small numbers of patients, often with several genetic groups in a sample. In the present study we have concentrated on a single genetic group and have examined over 100 patients with AD RP. The fact that we had to call for volunteers for lengthy examinations during the working week has introduced some bias: there is an excess of females and of patients in the 20–50 age group (Table 1). Further, in order not to restrict our sample unduly we have included families in which a diagnosis of AD RP is very probable but the confirmatory evidence of male to male transmission is absent. Such families account for just over 50% of our patients. However, given the total number examined, these factors should not strongly bias the survey.

PROGNOSIS

It is commonly stated that the prognosis for visual acuity (VA) is better in AD RP than in AR and X-L disease,[9 10] though this has been disputed.[11] About 60% of our patients have a VA better than or equal to 6/12 by the age of 50, or after a duration of 40 to 50 years of the disease. This is a greater percentage than that quoted by Pearlman[11] and similar to that found by Jay[9] and by Fishman.[10]

The factors associated with loss of visual acuity are (1) the presence of a secondary change such as a lens opacity, macular oedema, or macular atrophy (filled symbols of Fig. 6), and (2) duration of night blindness. Analysis of how these factors are interrelated reveals that with increasing duration of disease there is an increased probability of one or other of the secondary changes. However, there is also an independent, if small, effect of duration.

Macular oedema is more often associated with visual loss when the duration of disease is short, and macular atrophy when it is long. It may be that macular atrophy is a late consequence of macular oedema, but it is also possible that it is the result of longstanding disease. Certain families have a very high incidence of these macular changes, whereas others have none; this may represent a genetic variation.

To assess the effect of field loss on life we have assumed that a central field of radius 10° with the IV/4 target represents the minimum field required by a patient to be independently mobile. In our sample 93% of the patients in the under-20 age group, 89% in the 20–40 age group, and 60% in the over 40 age group had a field greater than or equal to this.

CLASSIFICATION

From an examination of intrafamilial and interfamilial differences in the static perimetry data obtained from large families we have identified two subgroups of AD RP: in one there is severe and diffuse loss of rod function which in some regions coexists with relatively normal cone function; in the other loss of rod function is regional and accompanied by loss of cone function. We have designated the pattern of behaviour of the first subgroup by the letter D (which stands for diffuse loss of rod function) and the second by the letter R (which stands for regional loss of rod function). The letter U refers to those patients whom we have not placed in subgroups D or R. The classification depends on measurements of the state of *rod* function by static perimetry and not on observations of fundus appearance or Goldmann fields. These do not distinguish between the subgroups, both of which show regional pigmentation and regional cone losses.

With ERG measurements a very similar subgrouping could have been obtained independently. D patients do not have a rod a or b wave, but most do have a maximum cone b wave greater than 20 μV. Most R patients have both maximum rod and cone b waves greater than 20 μV. Only two cases in each of the subgroups classified by static perimetry would not meet these criteria.

The patients of Arden *et al.*[6] are included in the present survey, but the method of classification in the previous study was based solely on the presence or absence of the rod ERG: if absent, patients were placed in subgroup A, if present, in subgroup B. This means that A includes not only D patients with a sizeable cone ERG, but also those patients who do not have any ERG at all (U patients). The equivalence of the B and R subgroups is closer, though not exact. Two R patients have no rod ERGs and were classified by Arden *et al.*[6] as 'A2.'

The age of onset of night blindness is not a reliable indicator of D or R patterns, since onset before the age of 10 was reported not only by all D patients but also by a substantial number of U and even a few R patients. There is a better but far from exact correspondence between the R pattern of behaviour and onset after 20 years of age.

The distinctions between patterns D and R may arise in three possible ways: (1) they are different stages along a progressive course of deterioration; (2) they are different phenotypic expressions of the same basic gene defect; (3) they represent different gene mutations. The general constancy of a pattern of visual loss within large families over a wide range of ages supports the hypothesis of genetic heterogeneity.

Massof and Finkelstein[34] first proposed the distinction between severe and diffuse rod disease (type 1) and regional photoreceptor disease (type 2). Broadly our D patients conform to the description of type 1 and our R patients to type 2. However, there are some differences: a feature emphasised for type 1 is that the degree to which rod losses are greater than cone losses is a constant over the whole visual field. In terms of our data this would mean very little variation in the G-R index for different zones. This is not the case for our D patients (Fig. 2C). For some patients the index falls to values of less than 1 in some regions. This indicates that there is still some rod function left in these regions and that cone losses are 'catching up' with rod losses. Another difference is that for type 2 the characteristic region of loss is the mid periphery. Whilst this is true for most of our R families, in two the main region of loss is far-peripheral (e.g. see Fig. 10 in Ernst *et al.*[7]). In view of these differences and the possibility that AD RP consists of more than two disease forms it is probably not appropriate at this stage to make a complete identification between D and type 1 subgroups on the one hand, and R and type 2 on the other.

The D families appear to form a more homogeneous subgroup than the R ones. Variation in the region maximally affected by disease may indicate that the R families need to be further subdivided. Yet another pointer to possible heterogeneity in the R subgroup is the variation in rod ERG. In the R group there are three individuals from three families who produce ERGs of less than 20 μV to the blue flash, whereas R patients typically give more than 40 μV and many fall within the normal range (greater than 140 μV). Two of these patients report early onset of night blindness, and the other family members are severely affected and in the U category. More information, especially that derived from longitudinal studies, is needed to determine the basis of this heterogeneity.

Almost all our D and R patients were classified on an individual basis, though four exceptions were made in the case of three large families, where the characteristics of other family members were taken into account. However, in the case of small family units, such as families 675 and 9999 illustrated in Fig. 3, where an individual does not conform to the criteria laid down for classification (e.g., 675/17 and 9999/42) he or she has been assigned to the U category, even though his or her relative is placed in one of the subgroups (e.g., 675/13 and 9999/60) in the R subgroup. If we were to classify these U individuals according to the characteristics of their relatives, then the numbers in the D subgroup would rise from 13 to 16 and in the R subgroup from 28 to 34.

DISEASE MECHANISMS

Can we infer anything about the nature of the disease process at the cellular level for the two subgroups? The key feature of pattern D is the combination of very poor rod function throughout the retina with near normal cone function in some regions. This suggests that the major problem is in the rod system. The absence of any measurable rod ERG, including an a wave produced by the rods themselves, together with a relatively well preserved cone ERG, points to a defect in the rod transduction mechanism prior to the generation of the a wave. It is tempting to see the widespread rod disturbance as the primary condition of the disease with the progressive deterioration of the cones as a secondary phenomenon. This would explain why night blindness is perceived from infancy while major field losses are only apparent later in life, and why the pigmentation of the fundus has a regional appearance and is characteristic of late disease. Nevertheless our results do not exclude the possibilities that rod losses are regional early in life but become diffuse with time, that regional cone losses are part of the primary disease mechanism, and that cone abnormalities are occurring in areas where

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cone thresholds are normal. Our view of a primary rod transduction defect throughout the retina has yet to be tested.

In the R patients the disease appears to be affecting both types of receptor in a given region—sometimes more or less equally as judged by threshold behaviour (e.g., see Fig. 10, Ernst *et al.*[7]) and sometimes with the rods more severely affected (e.g., see 675/17 and 9999/42, Fig. 3). A comparison of the ERG and psychophysical data (see Arden *et al.*[6]) points to a disturbance of not only photoreceptors but also of postsynaptic layers. There is also evidence that the disease is not confined to retinal cells. R patients show an elevated osmotic fragility of their erythrocytes, whereas the fragility of the red blood cells of D patients is normal.[12]

Future advances in research on AD RP will come from the application of new tests such as fundus reflectometry to patients already investigated by the techniques described in this study, longitudinal studies, the investigation of young family members, and histopathological and biochemical studies from donor eyes of properly characterised patients. From such studies it should become clearer whether our attempt at classifying AD RP has a valid basis, whether it needs to be refined and extended, and what are the underlying pathogenetic mechanisms.

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References

1 Krill AE. Retinitis pigmentosa: a review. *Sight Sav Rev* 1972; **42:** 21–8.

2 Berson EL, Gouras P, Gunkel RD, Myrianthopoulos NC. Dominant retinitis pigmentosa with reduced penetrance. *Arch Ophthalmol* 1969; **81:** 226–34.

3 Massof RW, Finkelstein D. Rod sensitivity relative to cone sensitivity in retinitis pigmentosa. *Invest Ophthalmol Visual Sci* 1979; **18:** 263–72.

4 Massof RW, Finkelstein D. Two forms of autosomal dominant retinitis pigmentosa. *Doc Ophthalmol* 1981; **51:** 289–346.

5 Marmor MF. The electroretinogram in retinitis pigmentosa. *Arch Ophthalmol* 1979; **97:** 1300–4.

6 Arden GB, Carter RM, Hogg CR, *et al.* Rod and cone activity in patients with dominantly inherited retinitis pigmentosa: comparisons between psychophysical and electroretinographic measurements. *Br J Ophthalmol* 1983; **67:** 405–18.

7 Ernst W, Faulkner DJ, Hogg CR, Powell DJ, Arden GB, Vaegan. An automated static perimeter/adaptometer using light emitting diodes. *Br J Ophthalmol* 1983; **67:** 431–42.

8 Arden GB, Carter RM, Hogg CR, *et al.* A modified ERG technique and the results obtained in X-linked retinitis pigmentosa. *Br J Ophthalmol* 1983; **67:** 419–30.

9 Jay B. Hereditary aspects of pigmentary retinopathy. *Trans Ophthalmol Soc UK* 1972; **92:** 173–8.

10 Fishman GA. Retinitis pigmentosa: visual loss. *Arch Ophthalmol* 1978; **96:** 1185–8.

11 Pearlman JT. Mathematical models of retinitis pigmentosa: a study of the rate of progress in the different genetic forms. *Trans Am Ophthalmol Soc* 1979; **72:** 643–56.

12 Hussain AA, Voaden MJ. Studies on retinitis pigmentosa in man. II. Erythrocyte osmotic fragility. *Br J Ophthalmol* 1985; **69:** 126–8.

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A genetic linkage study of a kindred with X-linked retinitis pigmentosa

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SUMMARY A large kindred with X-linked retinitis pigmentosa (XLRP) was investigated clinically and by means of genetic linkage with a view to developing methods of carrier detection and early diagnosis. A restriction fragment length polymorphism, identified by recombinant DNA probe L1.28, showed close genetic linkage to XLRP in this kindred and is a potentially useful marker for the purposes of genetic counselling.

In 1965 a family was described, consisting of seven daughters and three sons, whose father had died after being certified blind from an unknown cause.[1] The three sons were normal and two had normal children; the third was unmarried. Each of the seven daughters had one or more sons suffering from retinitis pigmentosa (10 in all). Since then two of their daughters have had affected sons (Fig. 1).

Initially there was some doubt whether this family should be classified as X-linked retinitis pigmentosa (XLRP), as in no case did the carriers show a tapetal reflex, which was believed at that time to be the characteristic fundus appearance of the carrier state. In addition several of the proved carriers showed retinal pigment epithelial changes with associated visual loss, which was severe in some cases. It has been recognised since then that female carriers may show changes other than a tapetal reflex and may have a visual deficit.[2-4] The pattern of inheritance in this kindred, associated with severe visual deficit and choroidal atrophy in advanced disease in affected males and variable visual function in the females, is compatible with a diagnosis of XLRP. It is reasonable to assume that the blind progenitor of this family (I/1) suffered from XLRP, which has therefore now occurred in four generations.

X-linked retinitis pigmentosa is due to an abnormal gene on an X chromosome. Males with one

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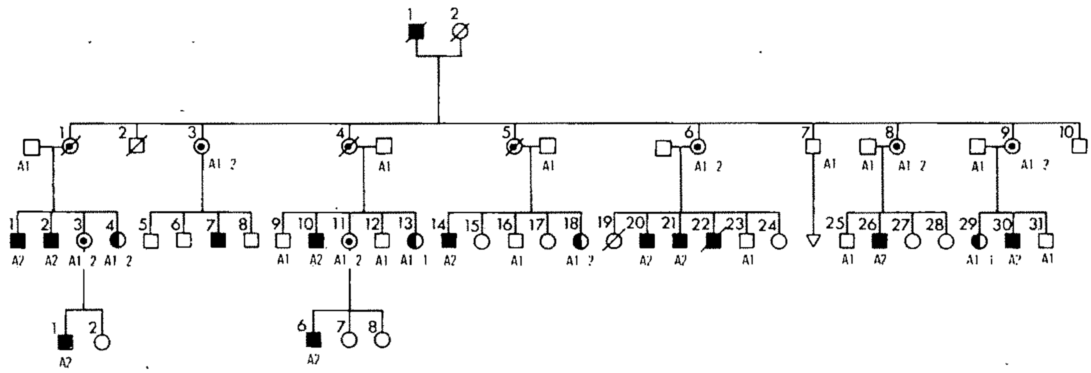


Fig. 1 *Pedigree of family RP22.*

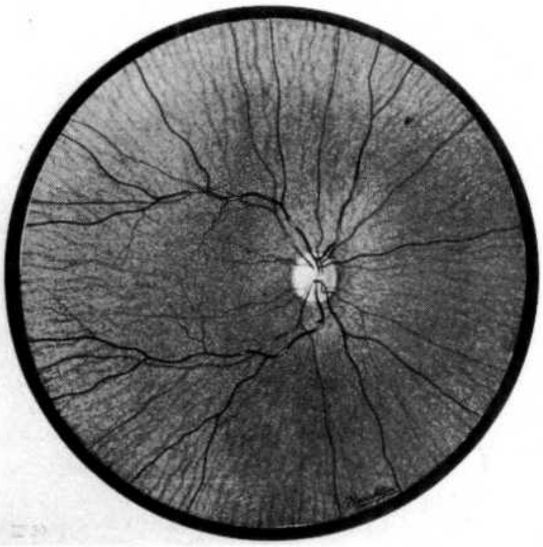


Fig. 2a

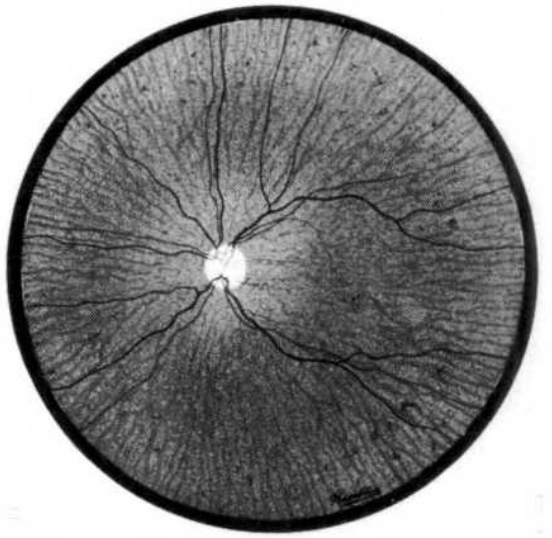


Fig. 2b

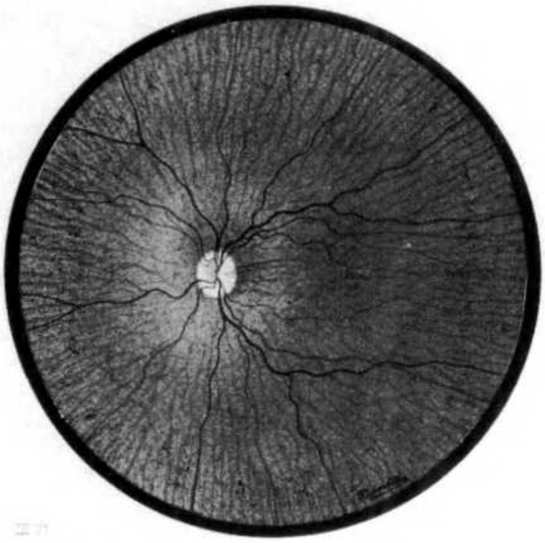


Fig. 2c

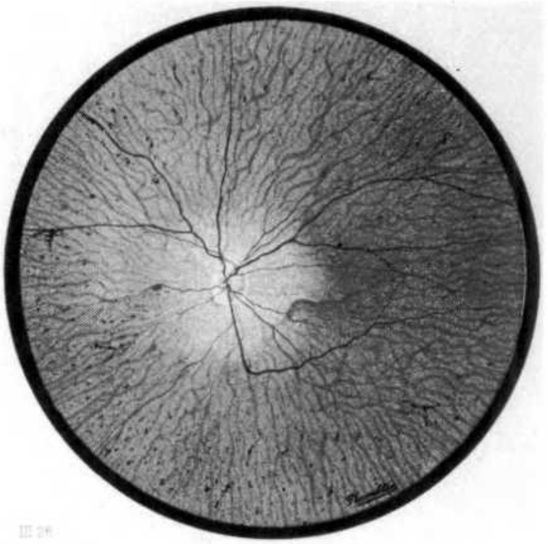


Fig. 2d

Fig. 2 *Fundus paintings of affected males:* (a) *III/30 aged 3 years,* (b) *III/22 aged 8 years,* (c) *III/21 aged 10 years,* (d) *III/26 aged 11 years,* (e) *III/1 aged 30 years.*

abnormal gene, whose normal chromosome complement includes one X and one Y chromosome, always express the disease. Affected males usually have night blindness in early childhood. When the disease has been present for some years, there is a characteristic fundus picture showing bone corpuscle pigmentation, attenuated retinal vessels, and pallor of the optic disc (Fig. 2); the diagnosis may be confirmed by electrodiagnostic tests. In some families it would be wrong to exclude the diagnosis before the early teens.

In X-linked disease there is no father to son transmission, since sons receive their X chromosome from their mother, but every daughter of an affected male receives an X chromosome from her father and is a carrier, termed an obligate heterozygote. In the absence of a corroborative family history mothers of

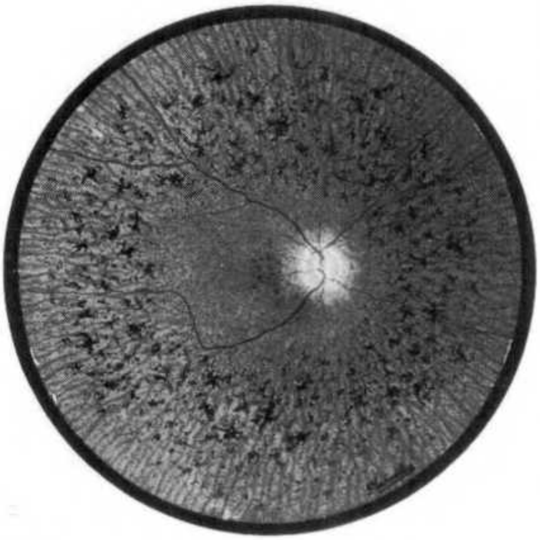


Fig. 2e

two or more affected males are also obligate heterozygotes, but mothers of one affected male are termed presumptive heterozygotes unless there are signs of the carrier state. The daughters of obligate heterozygotes are termed possible heterozygotes if they are clinically normal and obligate heterozygotes if they are clinically abnormal. XLRP is transmitted by heterozygotes, who have a 50% risk of having affected sons and the same risk of having daughters who will be carriers.

There is a wide spectrum in the expression of clinical signs in heterozygotes, which has been ascribed to the effect of random inactivation of the X chromosome.[5] According to the Lyon hypothesis one of the two X chromosomes of the normal female is inactivated early in embryogenesis. This inactivation occurs at random, and the inactivated X chromosome, which forms the Barr body, may be maternal or paternal in origin. Once inactivation has taken place, the daughter cells will retain the same active X chromosome. In particular, in a carrier female the cells which are destined to form the retina will comprise a proportion with a maternally derived active X chromosome carrying the gene for XLRP if she is the daughter of a heterozygote, and a proportion with a paternally derived active X chromosome carrying the gene for XLRP if she is the daughter of an affected male. These proportions will vary from one carrier to another, as a result of random inactivation of the X chromosome. This will result in symptoms having a variable age of onset or being absent altogether, and a clinical picture which can vary from one that is occasionally almost as severe as in the affected male, to cases where the retina, by chance, consists largely of cells in which only the normal X chromosome is active and no visual deficits are manifest.

The detection of the heterozygous state of XLRP is often very difficult, but several methods have proved

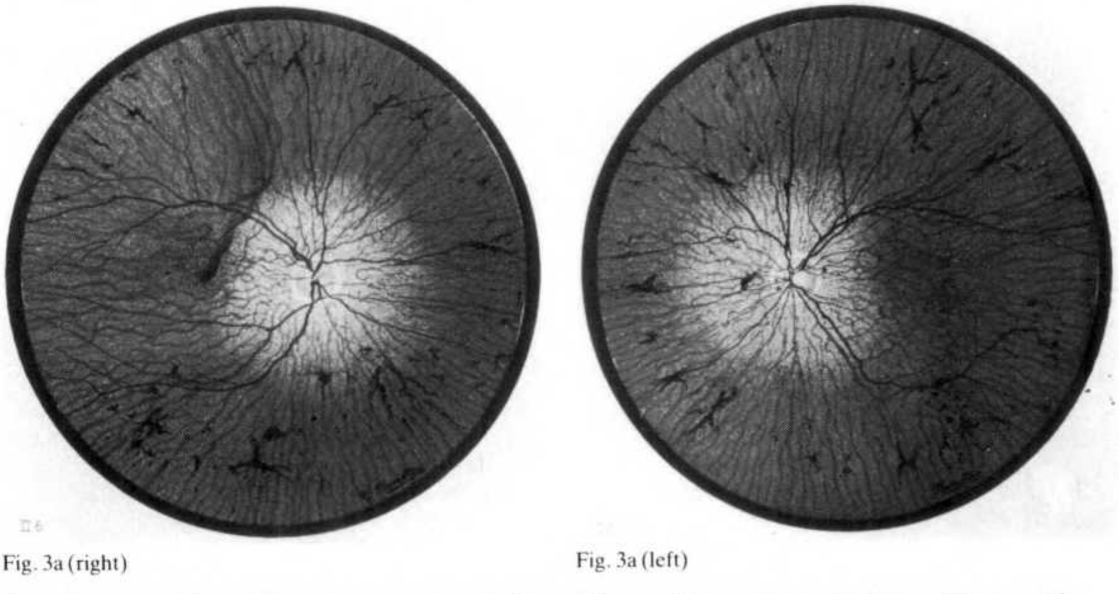


Fig. 3a (right)

Fig. 3a (left)

Fig. 3 *Fundus paintings of obligate heterozygotes:* (a) *II/6 aged 43 years, right and left eyes,* (b) *II/3 aged 54 years, right and left eyes,* (c) *II/1 aged 57 years, right and left eyes.*

helpful. Fundus changes can be identified in some carriers. A tapetal reflex or widespread retinal pigment epithelial changes with pigment migration are easily detected, but in most carriers the changes consist of small patches of pre-equatorial pigment epithelial thinning with or without pigment migration, or a grey appearance of the retinal pigment epithelium may also occur (Fig. 3). These latter changes may be slight, and especially in a blue-eyed individual the differentiation between a normal and an abnormal appearance of the retinal pigment epithelium may be difficult. Abnormalities in the electroretinogram (increase of the time to peak of the response to white light flickering at 30 Hz and/or a decrease in the amplitude of the scotopic b wave) have been demonstrated,[6] but the detection rate of carriers by this method is only 50%.[7] Variations from normal in flicker sensitivity have also been found both scotopically[8] and photopically,[9] but with this test only 60% of carriers are detected.

It is apparent therefore that more reliable and objective means of detecting the carrier state in an

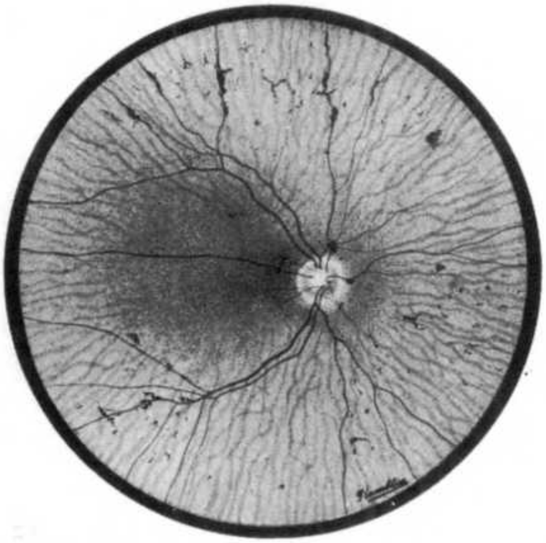


Fig. 3b (right)

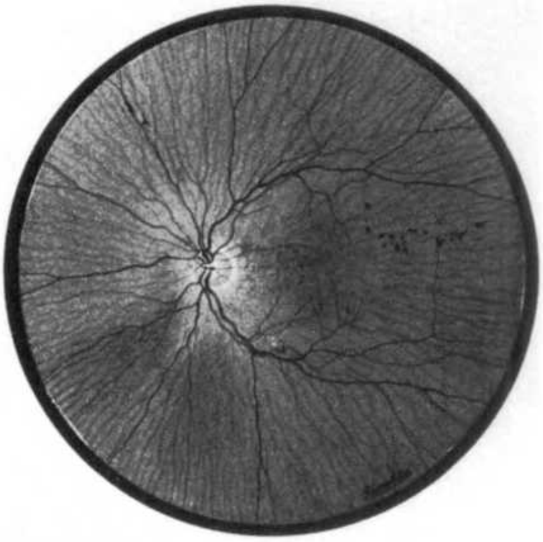


Fig. 3b (left)

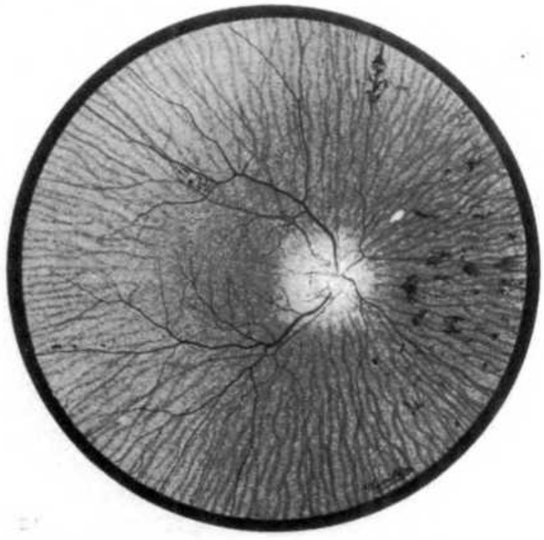


Fig. 3c (right)

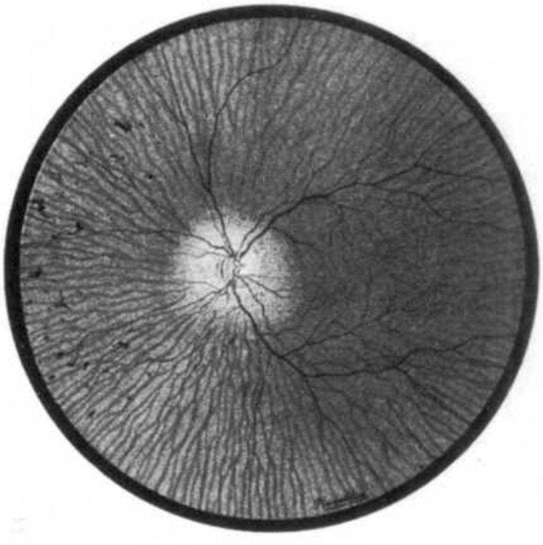


Fig. 3c (left)

individual female would be helpful to the clinician. Linkage studies seek to detect the presence of the disease by identifying a marker situated so close to the disease gene that the risk of crossover is minimal.[10] This method has the advantage that it can be performed at any age, since the genotype is established at conception and remains fixed throughout life. In the case of linkage markers identified by means of recombinant DNA probes there is the additional advantage of being independent of X chromosomal inactivation.

An X chromosome-specific recombinant DNA probe has been used that is specific to a site on the short arm of the X chromosome. The probe is a small sequence of DNA obtained by digestion of DNA from normal X chromosomes and cloned in a plasmid vector in order to provide sufficient quantities in a stable form for routine use. The linkage 'marker' is a variant nucleotide base (or bases), in the sequences flanking the probe, that occurs in a significant proportion of the population. The variant site can be detected only if it leads to a loss of one of the recognition sequences of a restriction endonuclease that normally cuts double-stranded DNA wherever it recognises a particular combination of 4–6 nucleotide bases. After electrophoretic separation of the endonuclease-digested DNA fragments the loss of a cleavage site is detected as an altered fragment length (restriction fragment length polymorphism—RFLP) by hybridisation to the radioactively labelled probe. It is the availability of large numbers of chromosome specific DNA probes, many of which can locate RFLP in nearby sequences, that makes it possible to map genes and develop RFLPs close enough to be used for presymptomatic diagnosis.[11]

In the present study females suspected of carrying the gene were investigated by several techniques in order to assess the probability of the heterozygous state being present. Blood from these females and other close relatives informative for linkage was subjected to analysis in an effort to find a linkage marker for the disease.

Material and methods

Ten females from the family were examined and tested, all of whom were the daughters of obligate heterozygotes. A history was taken and an ocular examination performed. Heterozygotes were identified by genetic criteria and recording ocular functions, including an electroretinogram (ERG), by the technique described by Arden *et al.*,[7] and flicker thresholds as described by Tyler and colleagues.[12 13]

Blood was taken from these 10 females and from a large number of other family members. DNA was extracted by the method of Kunkel and colleagues.[14] It was digested to completion with the restriction endonuclease TaqI and photographed after electrophoresis in 0·8% agarose gels and staining with ethidium bromide. Gel DNA was denatured in alkali, neutralised, and transferred to nitrocellulose filters by the method of Southern.[15] Filters were dried, baked, and hybridised overnight at 65°C in the presence of DNA from probe L1.28 labelled with ^{32}P-dTTP by nick translation. Filters were placed next to an intensifier screen and exposed to *x*-ray film for 3–7 days. L1.28 is a random X-chromosome specific sequence cloned in plasmid pBR322 and isolated from a genomic library by Pearson and his colleagues[16]; it has been shown to be located close to band Xp11.3 on the short arm of the X chromosome. Linkage was analysed by means of the computer program LIPED.[17]

Results

CLINICAL AND ELECTRODIAGNOSTIC STUDIES

The fundus appearance and electroretinographic and flicker results are summarised in Table 1. All cases were asymptomatic and had a normal visual acuity. Six of the 10 were thought to have an abnormal fundus appearance, and two of these were obligate heterozygotes by definition, having affected sons. The fundus changes consisted of patchy retinal pigment epithelial atrophy in the periphery with or without pigment migration. Only two of the five tested showed an abnormality on flicker testing, and this consisted of a uniform reduction in sensitivity across the whole frequency range (in which flicker can be detected) in the peripheral field. An ERG was recorded from three subjects and all were within normal limits, although one showed a low normal scotopic b wave amplitude. It was considered on the basis of these results alone that six of the 10 persons tested were presumptive heterozygotes.

Table 1 *ERG, flicker sensitivity, and fundus appearance in members of family*

Pedigree Number	*ERG*	*Flicker*	*Fundi*
III/3*	—	Normal	Abnormal
III/4	—	Abnormal in periphery	Abnormal
III/11*	Normal	—	Abnormal
III/13	Normal (but low b wave)	—	Abnormal
III/15	—	—	Normal
III/18	—	—	Abnormal
III/24	—	Normal	Normal
III/27	Normal	—	Normal
III/28	—	Normal	Normal
III/29	—	Abnormal in periphery	Abnormal

*Obligate heterozygote, having an affected son.
—Not done.

LINKAGE STUDIES

The results of the linkage studies with L1.28 are shown in Table 2 and Fig. 4. The two marker alleles are labelled A1 and A2, corresponding to DNA restriction fragments of length 12 kilobases (kb) and 9 kb respectively. It can be seen that all seven obligate heterozygotes in generation II carried allele A2 and at least six were heterozygous (A1–2) so that their offspring were informative for linkage. This means that the cosegregation or otherwise of alleles A1 and A2 with XLRP can be observed in their offspring. Allele A2 was found to be associated with XLRP in all 10 affected males and obligate heterozygous females in generation III, while allele A1 was associated with the seven tested unaffected males in generations II and III. It was assumed for the purpose of this study that 'at risk' females in generation III showing the characteristic fundus changes of carrier status and supported by other investigative techniques were presumptive carriers. Two 'at risk' females, shown to be carriers by these criteria, also received allele A2 from their mother, consistent with linkage between this allele and XLRP. However, two females (III/13 and III/29) showed fundus changes consistent with the carrier state and yet had marker status A1–1. Recombination may therefore have occurred between the XLRP and L1.28 loci in these cases. Four 'at risk' females in generation III were found to have normal results by fundus examination and other tests (Table 1), two of whom had alleles A1–1 and two of whom had A1–2 (allele A2 from mother). Since X-inactivation may lead to false negative results in 'at risk' females, the genetic status of females not manifesting the changes of carrier status was not inferred for the purposes of the linkage study.

The linkage results have been analysed both including and excluding the results from carrier females diagnosed clinically (Table 2). In both cases it is likely that probe L1.28 is closely linked to XLRP with maximum LOD scores greater than 3 at a distance less than 10 centimorgans (cM). This compares with the genetic length of the X chromosome of about 250 cM.[18] The current status of the linkage results in RP22 combined with other XLRP families is also shown in Table 2. The maximum likelihood value of the recombination fraction is 0·05, and the upper 95% confidence limit is 0·19, indicating that the error due to recombination is very unlikely to exceed 20%.

Table 2 *Linkage data for XLRP*

	RP22		*All XLRP*	
	Males only	*All*	*Males only*	*All*
LOD_{max}	5·10	3·78	6·32	6·81
θ_{max}	0·00	0·09	0·00	0·05
θ_{mean}	0·05	0·13	0·04	0·08
95% limits	0·0–0·19	0·02–0·30	0·0–0·15	0·01–0·19

Summary of the results of linkage analysis between L1.28 and XLRP in RP22 alone and combined with other XLRP families tested. The maximum likelihood (θ_{max}) and mean (θ_{mean}) values of the recombination fraction are shown together with the LOD scores corresponding to θ_{max} and the 95% confidence limits on θ. The analysis of the data used clinical information from males only and from males plus females identified as carriers on testing.

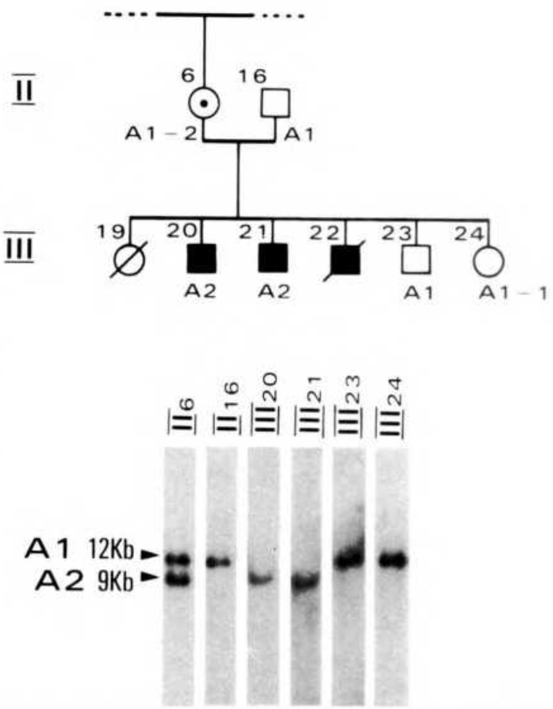


Fig. 4 *TaqI endonuclease digested DNA from members of an RP22 family, probed with recombinant DNA clone L1.28. The mother (II/6) is heterozygous for the L1.28 polymorphism, since she shows two restriction fragments with bands at 12 kilobases (kb; A1) and 9 kb (A2). The two affected sons (III/20, III/21) have the A2 allele, and the unaffected son (III/23) has the A1 allele. The daughter (III/24) showed no abnormality on clinical testing and is homozygous for allele A1.*

Discussion

CLINICAL RESULTS

The females who were examined as part of this study were seen over a period of several years, and hence the investigative techniques used to try and ascertain their genetic status have varied. The results obtained, however, serve to emphasise the low detection rate of the methods available at present. In our hands fundus examination still remains the most reliable means of diagnosis of the carrier state, especially within the context of a family history of X-linked retinitis pigmentosa. The detection of X-linked disease in an isolated individual and in the absence of a corroborative family history is at present extremely difficult and in some cases may be impossible.

LINKAGE RESULTS

Analysis of the linkage results in this family (identified at Moorfields Eye Hospital as RP22) suggests that there is close linkage between recombinant DNA probe L1.28 and XLRP. Similar results have been found in four other XLRP families,[19 20] which is consistent with the gene in affected members of family RP22 being either identical with or closely linked to that causing XLRP in other families. The combined data from all families give 95% confidence limits for the distance between L1.28 and XLRP of 1–20 cM (θ=0·01–0·19) and a minimum error (mean) value of the recombination fraction of 0·08, representing about 92% accuracy. The assignment of the L1.28 locus to the proximal short arm of the X chromosome (in the region of band Xp11.3), suggests that the XLRP gene is in the same region. At present only some 40% of XLRP families are informative for the L1.28 polymorphism, and work is under way to try to extend this to a greater proportion of families. A predictive test with accuracy greater than 92% is most likely to be achieved by a combination of probes flanking the XLRP locus, though the ordering of closely linked loci is problematical. In addition to refining genetic distances one further source of uncertainty must be dealt with before the L1.28 polymorphism can be used clinically in all families, namely, the possibility of genetic heterogeneity. This problem does not arise with family RP22, within which linkage has been established, but it may do with other XLRP kindreds in which the possibility of XLRP loci not linked to L1.28 cannot be discounted until several more independent families have been analysed.

COMBINED USE OF CLINICAL AND LINKAGE DATA IN XLRP CARRIER DETECTION

The use of information based on linked genetic markers as an aid in the detection of heterozygotes in XLRP is of potential importance, especially since DNA polymorphisms are unaffected by X chromosome inactivation and are independent of age. As information from genetic linkage and from clinical tests is essentially independent, it should be possible to combine the two sets of information quantitatively to allow a more accurate prediction than is possible from either set of data alone. This is already possible for such disorders as the X-linked muscular dystrophies, but unfortunately no accurate estimates exist for the likelihood of an XLRP heterozygote being classified as normal on the basis of clinical tests.

Until such information exists it is probably preferable to regard genetic linkage as strongly supportive of clinical tests when both predict the heterozygous state, while a prediction of normality would give a comparably strong reassurance, with an error unlikely to exceed 10%. In individuals at high genetic risk who show unequivocal clinical features of the heterozygous state, but are predicted by linkage to be normal (for example, III/13 and III/29 in the present kindred), it is advisable to rely on the clinical evidence. Comparable caution is wise in advising those clinically normal female relatives whose genetic linkage evidence predicts that they have received the XLRP gene.

Where an obligate or presumptive heterozygote is pregnant and the fetus is known to be male, genetic linkage data may allow prediction as to whether the fetus has or has not inherited XLRP. Since both fetal sex and fetal DNA polymorphisms (including L1.28) can be reliably detected by chorion biopsy in the first trimester of pregnancy, it is important that those women in whom the prediction could be applied and who would wish for such testing are fully informed and investigated prior to embarking on a pregnancy.

Finally, it should be stressed that application of genetic linkage in prediction requires study of the family unit, not just an individual, an added factor in favour of studies being done before they are actually needed in making decisions regarding childbearing. Since full accuracy of prediction may require the availability of affected individuals or spouses in older generations, serious consideration should be given to obtaining samples from such individuals during their lifetimes, so that the opportunity for prediction in the younger generations is not lost.

We thank Mr Barrie Jay and Professor A C Bird, who examined the fundi of members of this family, and Professor G B Arden and Dr W J K Ernst, who allowed electroretinography and flicker sensitivity measurements to be performed in the Electrodiagnostic Department at Moorfields Eye Hospital.

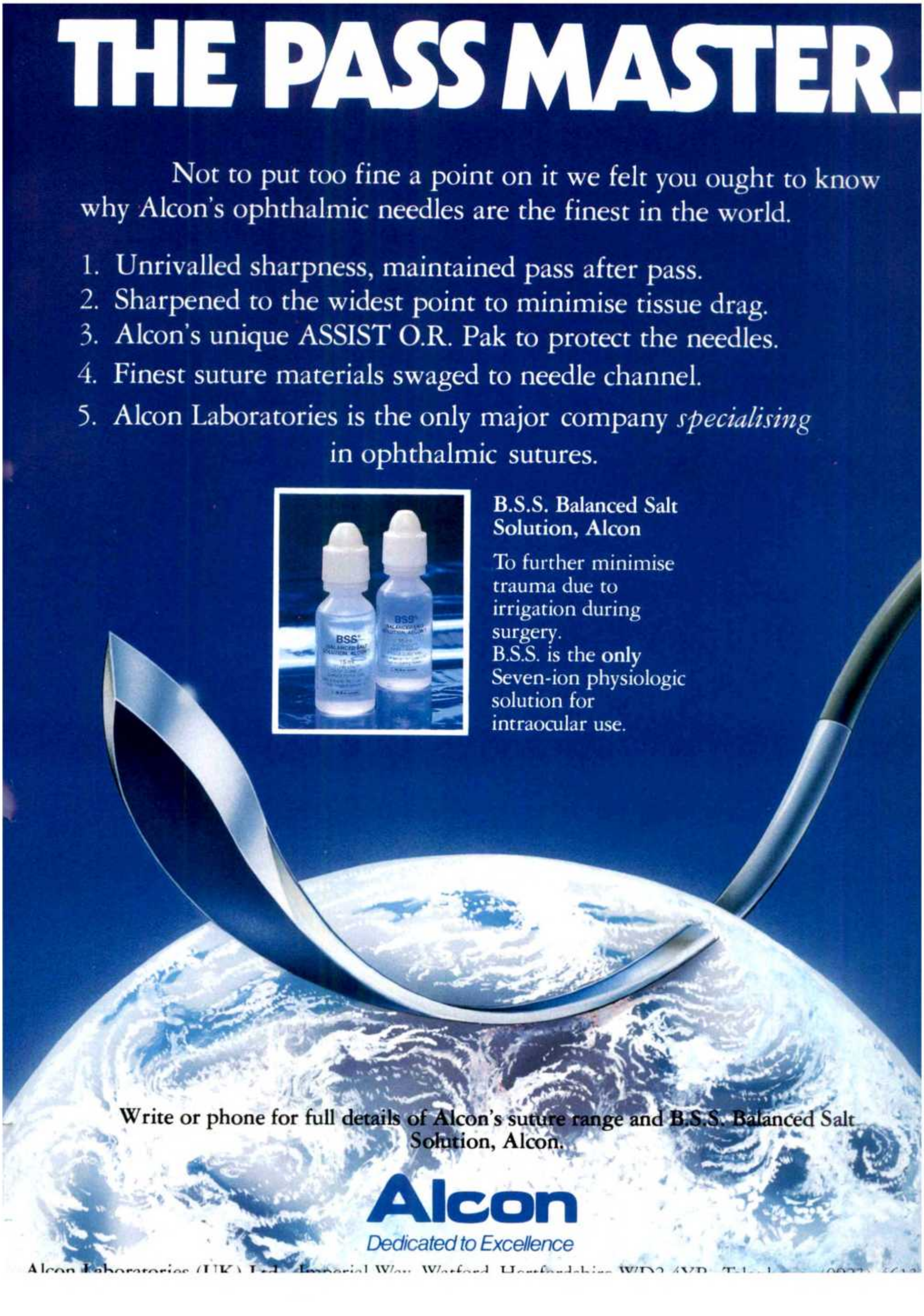
Dr S S Bhattacharya was generously supported by the Sir Jules Thorn Charitable Trust, and the Gwent Association for the Blind funded travelling and transport costs. This study was also supported by: MRC Grant G80/0986/7/N; a grant from the British Retinitis Pigmentosa Society, and a grant from the National Retinitis Pigmentosa Foundation, Inc.

References

1 Hoare GW. Chorioretinal dystrophy. *Br J Ophthalmol* 1965; **49:** 449–59.

2 Bird AC. X-linked retinitis pigmentosa. *Br J Ophthalmol* 1975; **59:** 177–99.

3 Kobayashi F. Genetic study on retinitis pigmentosa. *Jpn J Ophthalmol* 1960; **4:** 82–8.



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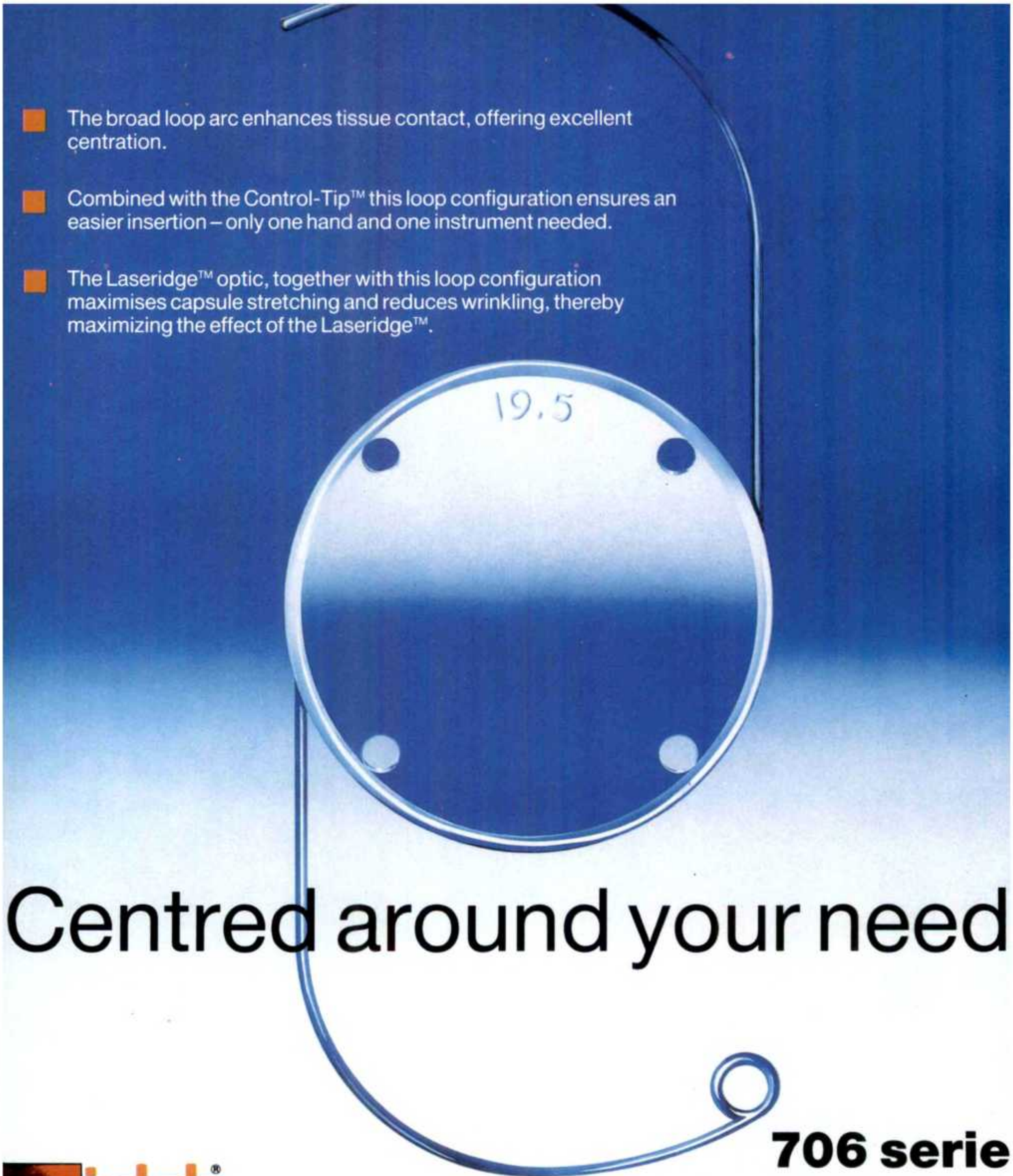

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4 McKenzie DS. The inheritance of retinitis pigmentosa in one family. *Trans Ophthalmol Soc NZ* 1951; **5:** 79–82.

5 Lyon MF. Gene action in the X-chromosome of the mouse. *Nature* 1961; **190:** 372–3.

6 Berson EL, Gouras P, Gunkel RD, Myrianthopoulos NC. Rod and cone responses in X-linked retinitis pigmentosa. *Arch Ophthalmol* 1979; **81:** 215–25.

7 Arden GB, Carter RM, Hogg CR, *et al.* A modified ERG technique and the results obtained in X-linked retinitis pigmentosa. *Br J Ophthalmol* 1983; **67:** 419–30.

8 Ernst WJK, Clover GM, Faulkner DJ. X-linked retinitis pigmentosa: reduced rod flicker sensitivity in heterozygous females. *Invest Ophthalmol Visual Sci* 1981; **20:** 812–6.

9 Ernst WJK, Tyler CW. Differential temporal visuogram losses associated with genetic classes of retinitis pigmentosa. *ARVO Suppl* 1982; **22:** 137.

10 Wright AF, Bhattacharya SS, Price WH, *et al.* DNA probes in X-linked retinitis pigmentosa. *Trans Ophthalmol Soc UK* 1983; **103:** 467–74.

11 Weatherall DJ. *The new genetics and clinical practice.* Oxford: Nuffield Provincial Hospitals Trust, 1982.

12 Tyler CW, Ernst WJK, Lyness AL. Photopic flicker sensitivity losses in simplex and multiplex retinitis pigmentosa. *Invest Ophthalmol Visual Sci* in press.

13 Tyler CW. Specific deficits of flicker sensitivity in glaucoma and ocular hypertension. *Invest Ophthalmol Visual Sci* 1981; **20:** 204–12.

14 Kunkel LM, Tantravahi U, Eisenhard M, Latt SA. Regional localization on the human X of DNA segments cloned from flow sorted chromosomes. *Nucleic Acids Res* 1982; **10:** 1557–78.

15 Southern EM. Detection of specific sequences among DNA fragments separated by gel electrophoresis. *J Mol Biol* 1975; **98:** 503–17.

16 Pearson PL, Wieacker P, Bakker B, Prins HA. A restriction site polymorphic marker for the short arm of the X chromosome. *Clin Genet* in press.

17 Ott J. Estimation of the recombinant fraction in human pedigrees: efficient computation of the likelihood for human linkage studies. *Am J Hum Genet* 1974; **26:** 588–97.

18 Ropers H-H, Wieacker P, Wienker TF, Davies K, Williamson R. On the genetic length of the human X chromosome. *Hum Genet* 1983; **65:** 53–5.

19 Wright AF, Bhattacharya SS, Price WH, *et al.* A genetic linkage study of X-linked retinitis pigmentosa. *J Med Genet* 1984; **21:** 140.

20 Bhattacharya SS, Wright AF, Clayton JF, *et al.* Close genetic linkage between X-linked retinitis pigmentosa and a restriction fragment length polymorphism identified by recombinant DNA probe L1.28. *Nature* 1984; **309:** 253–5.

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Control of postoperative astigmatism

A D ATKINS AND M J ROPER-HALL

From the Birmingham and Midland Eye Hospital

SUMMARY Thirty-six eyes with excessive astigmatism following cataract extraction via a corneal section were subjected to suture adjustment. This was performed six to eight weeks postoperatively under topical anaesthesia. The cases were selected from a large volume of corneal section cases because they had over 3·0 dioptres astigmatism. We reduced astigmatism significantly in the majority. There were no serious complications.

Postoperative astigmatism has demanded the attention of surgeons for decades.[1-4] The subject has been recently reviewed.[5] Some surgeons have avoided corneal sections because of unacceptable and unpredictable postoperative astigmatism.[6] However, apart from this aspect the corneal section has considerable advantages. There is negligible bleeding and haemostasis is not necessary. Visibility is excellent during surgery, particularly during insertion of implants. As the wound is 180°, lifting the corneal flap does not cause the lower cornea to bend inwards during the insertion of an implant. The wound can be made (and proved to be) watertight at the end of surgery. Peripheral anterior synechiae to the wound, which might lead to glaucoma and contact between implants and corneal endothelium, are prevented. Contact lenses can be fitted early and are more comfortable owing to the lack of conjunctival oedema. Cataract extractions in patients with functioning filtration blebs are best performed via the corneal route, and some would argue that all chronic simple glaucoma patients should have their cataracts removed through a corneal section.[7] (Cairns J E, personal communication).

The major objections to the corneal section are slower healing and increased astigmatism. Inert sutures can be left to support the tissues until firm healing has been established. This article shows that postoperative astigmatism can be controlled in corneal section cases.

Patients and methods

Thirty-six patients underwent cataract surgery by a two-step incision with one preplaced 8/0 (0·3 metric) silk suture at the 12 o'clock meridian and a postplaced 10/0 (0·2 metric) continuous polyamide suture tied with buried knots at each end (Fig. 1). The technique has been described before.[8] The interrupted suture is usually removed 10-14 days after surgery at an out-patient visit.

During the 6-8 week period these 36 patients were refracted and found to have astigmatism greater than 3·0 dioptres. They were subjected to adjustment of their continuous suture at the slit-lamp by one of the authors. By this time the corneal epithelium had covered the suture. The epithelium overlying each suture was broken, and the subepithelial portions of the suture were gently grasped with fine plain Pierse forceps and eased loop by loop towards the axis of the positive cylinder (Fig. 1), commencing from each

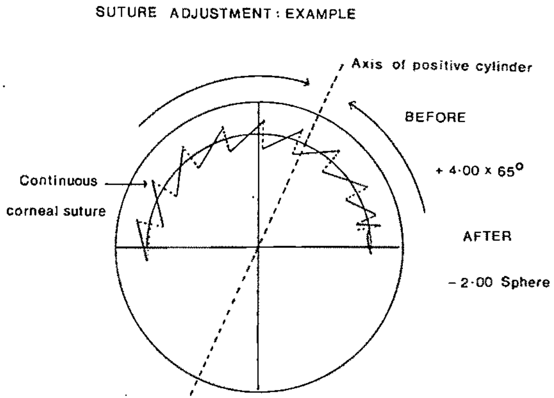
SUTURE ADJUSTMENT: EXAMPLE
Axis of positive cylinder
BEFORE
+ 4·00 x 65°
AFTER
− 2·00 Sphere
Continuous corneal suture

Fig. 1 *An example of suture adjustment. This patient had 4·0 dioptres astigmatism at six weeks postoperatively. His continuous suture was eased towards the positive axis of 65° with an immediate result of no astigmatism. This result was maintained until final follow-up of 38 months.*

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end of the continuous suture. The refraction was then immediately rechecked, and if necessary the suture was adjusted again. This technique is simple to master, but because of the slight risk of breaking the suture we delayed adjustment until the sixth or preferably eighth postoperative week. A one-week course of topical antibiotics is recommended as prophylaxis against infection. The patients were followed up with serial refractions, and when stability was reached spectacles were ordered.

Results

There were 36 patients; 16 males and 20 females. Their ages ranged from 61 to 81 years with an average age of 70·6 years. Follow-up ranged from six to 38 months, average 12 months. Two cases (5 and 6 dioptres at final follow-up) were resutured successfully (see 'Discussion'). The results are best presented with figures considering cylindrical power, axis, and final visual acuity.

CYLINDRICAL POWER

Fig. 2 shows how the power of the cylinders changed before and immediately after suture adjustment. It can be seen from the scattergram that all but one case were the same or had reduced astigmatism. Thirty-three cases (92%) showed a reduction. However, 11 cases (30%) still had more than 3·0 dioptres astigmatism. When the final cylindrical power is compared with that before suture adjustment (Fig. 3), it can be seen that 32 cases (89%) had 3·0 dioptres or less of astigmatism. Cases numbered 1 and 2 on the scattergram were resutured (see 'Discussion') with a successful outcome.

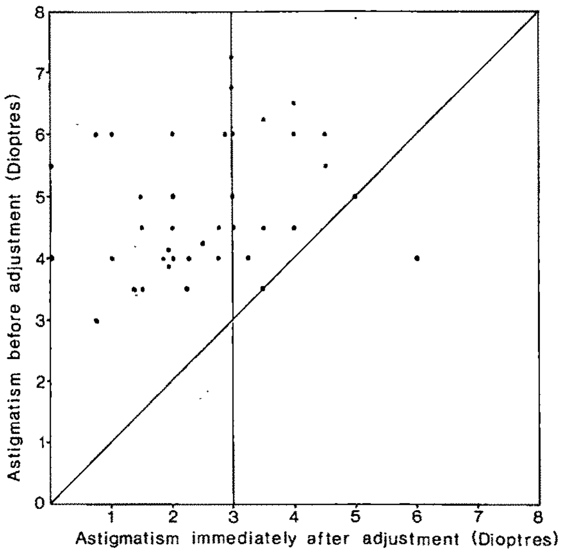

Fig. 2 *Scattergram showing the astigmatism before and immediately after suture adjustment. The diagonal represents no change in cylindrical power; above the line represents decrease of power, whereas below the line represents an increase. The vertical line separates cases of less and more than 3 dioptres after adjustment.*

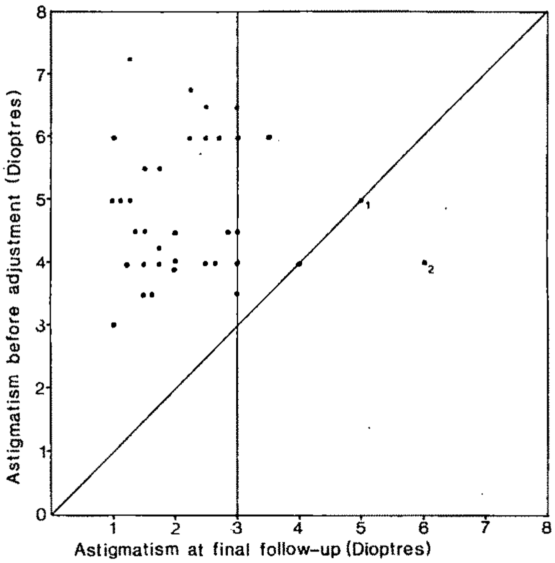

Fig. 3 *Scattergram showing the astigmatism before adjustment and at final follow-up. Again results above the diagonal line represent a decrease in cylindrical power, whereas those below it represent an increase. Cases numbered 1 and 2 were resutured with success (see 'Discussion'). Note that all but four cases had 3·0 dioptres or less of astigmatism.*

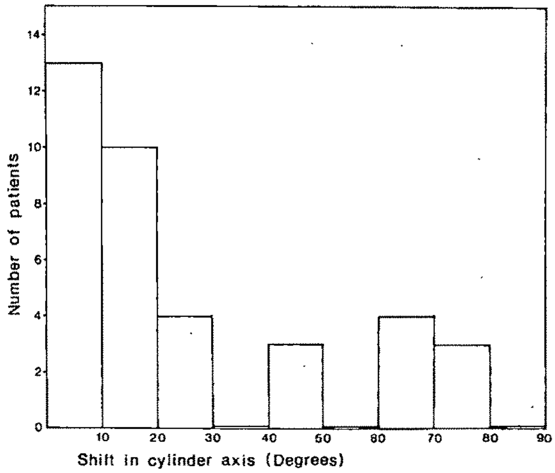

Fig. 4 *Histogram showing how the axes of the cylinders shifted before and immediately after suture adjustment. It can be seen that, although the majority of cases had less than 20° shift of axis, a minority had shifts up to 90°.*

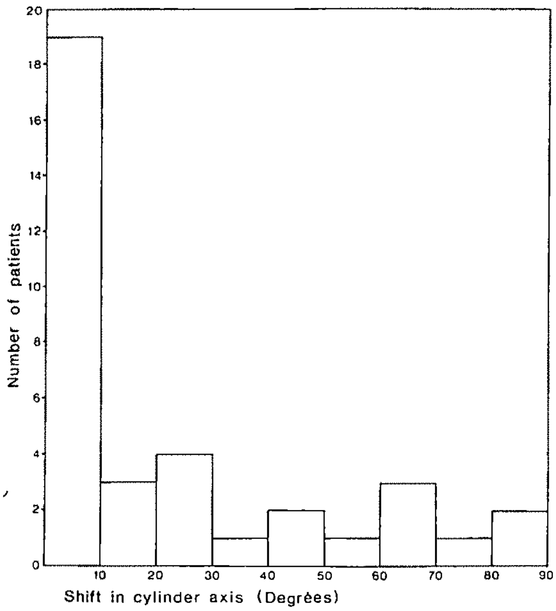

Fig. 5 *Histogram showing how the cylinder axis shifted from immediately after suture adjustment until the final follow-up. It can be seen that an even larger majority remained within 20° of that immediately after adjustment, with more falling into the 0 to 10° group.*

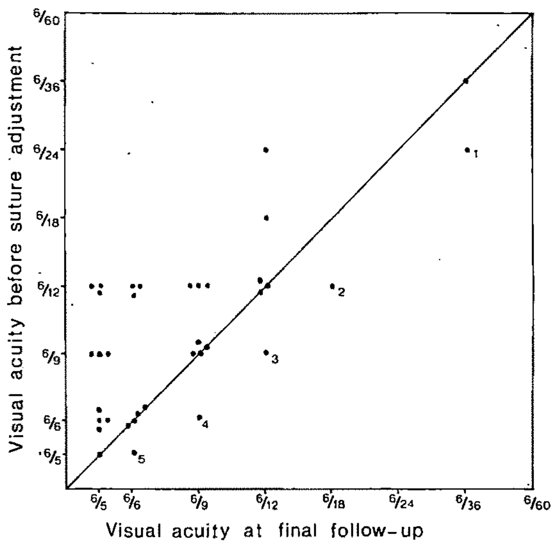

Fig. 6 *Scattergram showing the improvement of visual acuities (corrected) from before suture adjustment to final follow-up. Those cases on the diagonal line experienced no change in visual acuity. Those cases above the line showed improvement in vision, whereas those below the diagonal line show a deterioration. These five cases with reduced acuity are numbered. Case 1 had senile macular degeneration, cases 2 and 3 cystoid macular oedema, and cases 4 and 5 presumed cystoid macular oedema.*

CYLINDRICAL AXIS

Fig. 4 shows the shift of cylindrical axis before and immediately after suture adjustment. Twenty-three cases (64%) showed 20° or less of axis shift. However, there was a scattering of cases showing shifts up to 90°. For the sake of simplicity we have not shown data correlating the cylindrical power with the cases of nearly 90° axis shift. In Fig. 5 we can see how many cases showed further shift in axis: 19 cases (53%) had 10° or less of shift and 22 cases (61%) less than 20°. There were still some cases shifting up to 90°.

VISUAL ACUITY

All the acuities recorded were with correction. Fig. 6 shows the visual acuities before adjustment and at final follow-up. It is interesting to observe that 21 cases (56%) showed improved visual acuities after adjustment despite the fact that all acuities were with best correction. Ten cases had the same acuity. The acuities of five patients deteriorated during follow-up; this seemed to be unrelated to the adjustment. One had senile macular degeneration, two had cystoid macular oedema (one of these recovered to 6/12 vision at final follow-up), and in two cystoid macular oedema was postulated but not proved by fluorescein angiography (final acuities of 6/6 and 6/9).

COMPLICATIONS

Broken suture—2 cases (5·5%). There were two cases of accidental breaking of the continuous 10/0 nylon suture. Both sutures were subsequently removed. The first case was left with 4·0 dioptres astigmatism with 6/5 Snellen acuity. The second stabilised to +1·25 dioptres astigmatism with an acuity of 6/12.

Failed adjustment—2 cases (5·5%). In these cases repeated adjustments failed and the suture was removed. After suture removal the astigmatism remained unacceptable (5·0 and 6·0 dioptres) and did not decrease with time. Both were subjected to surgery consisting of inserting buried tensioning nylon 9/0 sutures around the axis of the negative cylinder, with the intention of leaving them in situ. They achieved final results of +2·50 dioptres with an acuity of 6/6 at 9 months and +3·00 dioptres and a visual acuity of 6/5 at five years after the suturing procedure (see 'Discussion').

There were no other complications–in particular no aqueous leaks or infections were seen following suture adjustment.

Discussion

The advantages and disadvantages of the corneal cataract incision have been mentioned in the introduction. Astigmatism can be troublesome, though less so with surgical experience. Our results show that a high proportion (89%) of these unfortunate patients had their astigmatism reduced to 3·0 dioptres or less by this simple procedure. One broken suture and two failed adjustments accounted for the remaining three cases with more than 3·0 dioptres astigmatism. Two of these cases (5 and 6 dioptres respectively) were successfully corrected by resuture. This procedure is described by the authors.[9]

The shift in cylindrical axis recorded has been shown in a simple form in the histograms (Figs. 4 and 5). The situation becomes difficult to display when the axis shifts approximately 90°, as the effect of the adjustment is additive, but this was not central to the point of this article. Essentially most cases kept the cylindrical axis they had before adjustment.

The visual acuity fluctuations depicted in (Fig. 6) show essentially that the procedure improves acuity in the majority of cases, and in those cases where the visual acuity fell it was not related to the adjustment.

Readers may be concerned at the risk of breaking the continuous suture during adjustment. We found the procedure straightforward and safe provided that: (1) a fine non-toothed forceps is used, pulling in the long axis of the suture; (2) the patient is relaxed and looking at the fixation lamp of the slit-lamp with his other eye; (3) the patient's eyelids are not inadvertently touched with the forceps, with resulting reflex blepharospasm.

CONCLUSION

A safe, effective, and reliable method of reducing postoperative astigmatism in corneal section cataract patients is described. With this suture adjustment technique available, the advantages of corneal section cataract surgery deserve greater consideration.

Our thanks are due to Dr A J Kempster and Mr A P Tompkin, who performed the majority of the many refractions required, and also to Miss P Quinn, who typed the manuscript.

References

1 Bedrossian PB, Sabata G, Troutman RC. Induced astigmatism as a result of surgery. In: Luntz MH, Shapiro HA. *Proceedings of the 1st South African international ophthalmological symposium 1969.* Durban: Butterworth, 1969: 219–25.

2 Jaffe N. Corneal astigmatism change related to cataract incision location. In: *Proceedings of the 2nd Biennial cataract surgical congress.* Miami: Educational Press, 1971: 366–9.

3 Troutman RC. Corneal astigmatism change related to cataract incision location. In: *Proceedings of the 2nd Biennial cataract surgical congress.* Miami: Educational Press, 1971: 370.

4 Troutman RC. Microsurgical control of corneal astigmatism in cataract and keratoplasty. *Trans Am Acad Ophthalmol Otolaryngol* 1973: **77**: 563–72.

5 Roper-Hall MJ. Control of astigmatism after surgery and trauma. *Br J Ophthalmol* 1982; **66**: 556–9.

6 Jaffe NS. *Cataract surgery and its complications.* St Louis: Mosby, 1976: 83–98.

7 Rothkoff L, Biedner B, Blumenthal M. The effect of corneal section on early increased intraocular pressure after cataract extraction. *Am J Ophthalmol* 1978; **85**: 337–8.

8 Roper-Hall MJ. Intraocular lens with intracapsular cataract extraction. *Trans Ophthalmol Soc UK* 1981: **101**: 56.

9 Roper-Hall MJ, Atkins AD. Control of astigmatism after surgery and trauma: a new technique. *Br J Ophthalmol* 1985; **69**: 352-59.

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Control of astigmatism after surgery and trauma: a new technique

M J ROPER-HALL AND A D ATKINS

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SUMMARY Five patients were subjected to a new technique designed to correct high astigmatism not responding to suture removal or adjustment. The method is described and its use illustrated in five case histories. Four of the five cases were successfully treated. The reasons for the one failure are discussed. All procedures were uncomplicated. The technique is simple, safe, and reversible.

Despite safe surgical technique and generally accurate microsurgical wound closure some patients are found to have unacceptably high astigmatic errors. Some of these errors are amenable to the selective removal of overtight sutures, the adjustment of a continuous suture, or both.[1]

However, in a number of cases of astigmatism these methods cannot be applied. There are several possible reasons: (1) All the sutures have already been removed. (2) The wrong sutures have been removed, making the astigmatism worse. (3) The initial injury caused so much scarring and traction that suture removal has no effect. (4) The sutures are buried, as in a standard corneoscleral section, under a limbal-based conjunctival flap. (5) Adjustment of a continuous suture has failed.

In these unfortunate patients further surgery may be required. Fyodorov[2] reintroduced methods of keratotomy and has described its use in the correction of astigmatism as well as refractive errors. Final results have not been predictable, with high errors, and there may be complications.[3] Any surgical procedure involving cutting the cornea or removing a wedge[3] is irrevocable, and if the outcome is unsatisfactory it is not reversible.

Material and methods

CASE SELECTION

Our five cases consist of: (1) One case of astigmatism following keratoplasty (case 1). (2) Three cases of astigmatism following routine cataract extraction with four-loop Binkhorst intraocular lens insertion (cases 2, 3, and 4). All three were subjected to adjustment of their continuous sutures,[1] but the procedure failed to correct their astigmatism. Two of these cases were part of a group of 36 such adjustment cases; the remainder were managed successfully without resorting to resuture. The results of these 36 cases are reported separately.[4] (3) One case of penetrating trauma to corneosclera and lens. This case stands out as a separate problem and is presented last.

METHODS

After appropriate anaesthesia (our patients were treated under general anaesthesia) a superior rectus bridle suture is placed to control the position of the eye. Interrupted 9/0 nylon sutures are placed at 2/3rds depth in the clear peripheral cornea at and around the axis of the negative cylinder. The lengths of bite were 2–3 mm. For example: refraction +2·00 D.sp/−7·00 D.cyl axis 60° (Fig. 1).

Tight 9/0 nylon sutures will be placed as shown. They are placed in two rows on both ends of the 60° meridian. The first tie of the suture has three throws and is pulled tight enough to show stress in the cornea. This steepens the cornea sufficiently to convert the minus to a plus axis in the same meridian. An assistant holds the tie while the knot is completed with single throws to make it secure. The excess is cut off short with a sharp blade and the suture rotated to bury the knot in the suture track. Several knots are inserted, with the aim of overcorrecting the astigmatism at the time of surgery. This could well result in a 10–15 dioptre change in astigmatism and cause the eye in this example to have an early postoperative cylinder of 5 dioptres with a plus axis at the same 60° meridian—that is, a change of 12 dioptres. This allows for the reduction in the cylinder, as the effect degrades during a four to six weeks postoperative course. If necessary further adjustment is made after

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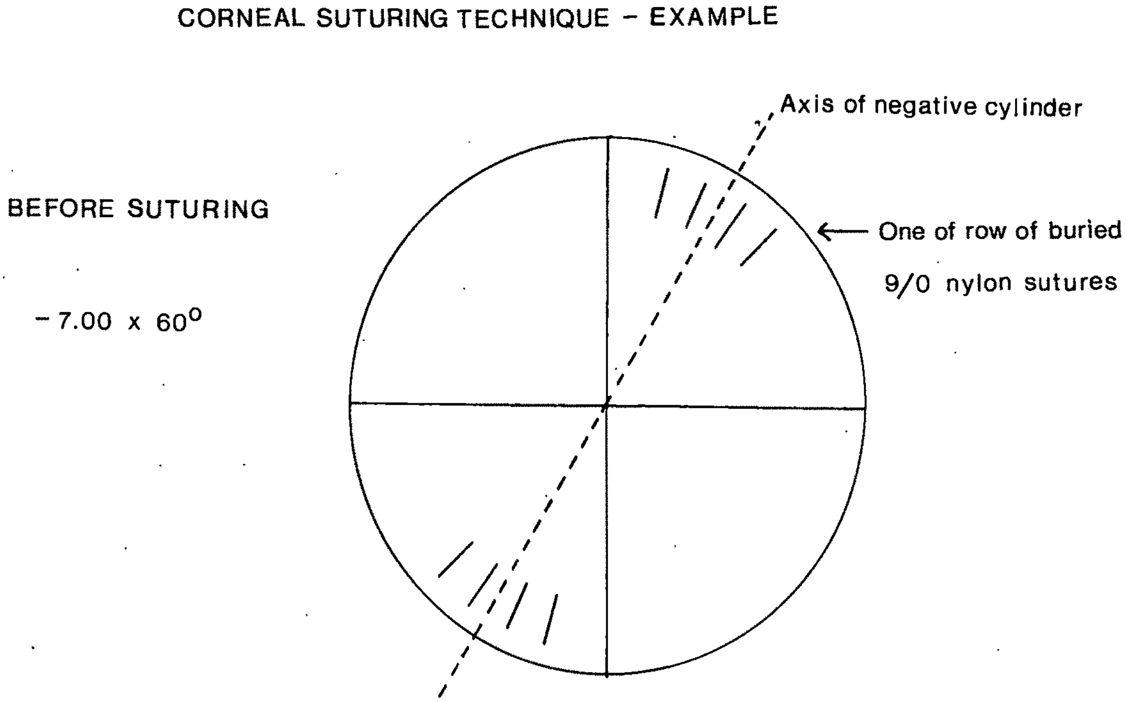
CORNEAL SUTURING TECHNIQUE - EXAMPLE
BEFORE SUTURING
- 7.00 x 60°
Axis of negative cylinder
One of row of buried 9/0 nylon sutures

Fig. 1 *Example of corneal suturing technique. A cylinder of −7·00×60° would be treated by placing 9/0 nylon sutures tightly in clear cornea around the 60° axis (i.e., the axis of the negative cylinder) to steepen this meridian. The knots must be buried.*

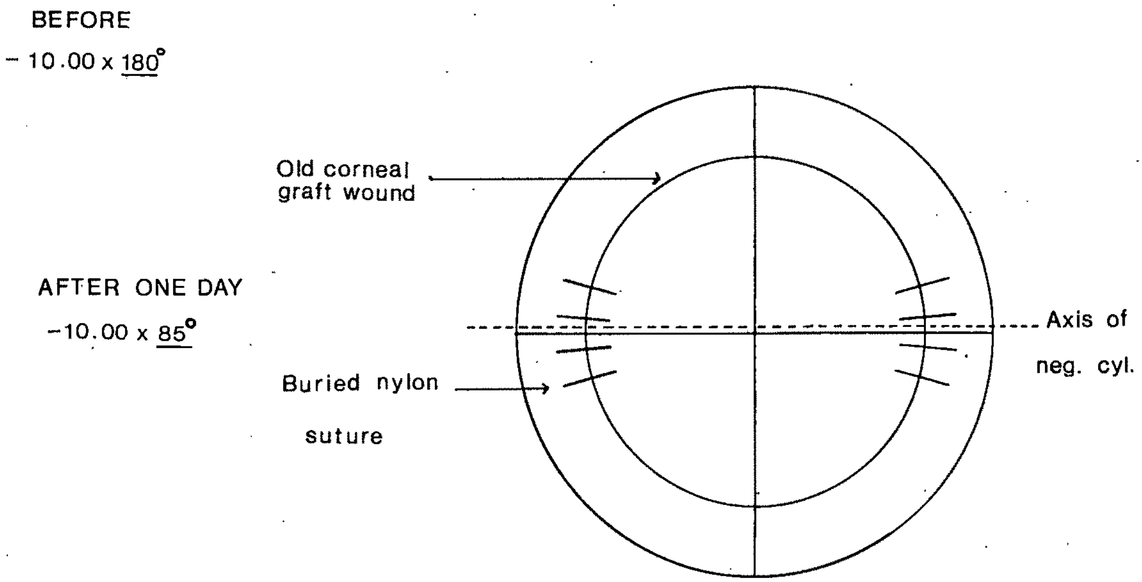

Fig. 2 *Case 1. A female aged 28 years, underwent penetrating keratoplasty in June 1981 for corneal scarring following herpes zoster ophthalmicus. In February 1982 indiscriminate removal of all sutures in an attempt to correct 5·00 dioptres astigmatism actually produced a 10·00 dioptre cylinder axis 180°. Interrupted sutures as shown shifted the axis to 85°—a change in astigmatic power of 20·00 dioptres.*

not less than four weeks by removing some of the newly placed individual sutures, which are now in the axis of the *positive* cylinder, and checking the refractive error between each removal until a satisfactory refraction is obtained. Experience has shown that it is often wise to make this adjustment over a period of a few weeks, only a single suture being removed at any one time. The optimum time for this adjustment seems to be between four and eight weeks after the tensioning sutures have been placed. The remaining sutures are left in situ.

We must stress that the tensioning sutures are placed in the negative axis, with the aim of overcorrection, and delayed single suture removal is in the same axis, which is then positive.

We have found 9/0 nylon to be most reliable; with finer gauge, tension may not be sufficient before the suture breaks. It is wise to warn the patient that surgery is aiming at an overcorrection. The refraction should be observed during the early postoperative course and removal of sutures firmly resisted until this observation has been sufficient for early moulding to have become stable. This period serves a similar purpose to that described previously.[1]

Case reports

CASE 1 (Figs. 2, 3)
A female aged 28 years suffered right herpes zoster ophthalmicus with subsequent scarring. 10 June 1981: right penetrating keratoplasty, 7·5 mm. 18 February 1982: +4·25 D.sp/−5·00 D.cyl axis 100°= 6/18.

Unfortunately all the sutures were removed indiscriminately without reference to the axis of astigmatism, resulting in +3·00 d.sp/−9·00 D.cyl axis 20°. 21 June 1982: refraction still −0·50 D.sp/−10·00 D.cyl axis 180°.

Interrupted sutures were placed in her cornea (Fig. 2) under general anaesthesia round the axis of the negative cylinder. One day later: +6·50 D.sp/−10·00 D.cyl axis 85°—that is, a change of cylinder of 20·00 dioptres. Between one and six weeks later single sutures were removed in the axis of the *positive* cylinder until her refraction was plano/−2·00 D.cyl axis 70°.

She has subsequently retained the small cylinder, and on 9 June 1983, twelve months later, her refraction was −0·50 D.sp/−2·00 D.cyl axis 50°.

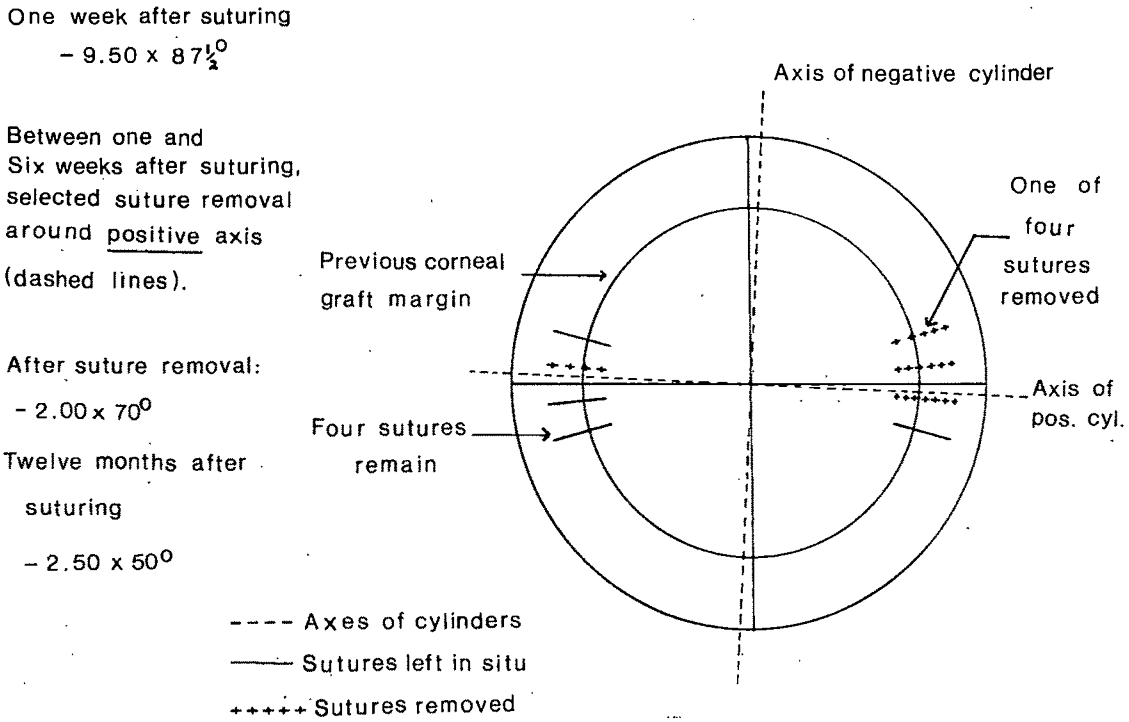
One week after suturing
- 9.50 x 87½°
Between one and Six weeks after suturing, selected suture removal around positive axis (dashed lines).
After suture removal:
- 2.00 x 70°
Twelve months after suturing
- 2.50 x 50°
Previous corneal graft margin
Four sutures remain
Axis of negative cylinder
One of four sutures removed
Axis of pos. cyl.
---- Axes of cylinders
—— Sutures left in situ
++++ Sutures removed

Fig. 3 *Case 1. Between one and six weeks after suturing, selected sutures (shown as dashed lines) were removed around the line of the* positive *axis. The cylinder was checked between each removal until her refraction revealed 2 dioptres of astigmatism at six weeks. A year after suturing her cylinder is −2·00×50°.*

COMMENT

The initial dramatic effect of the suturing can be seen, with a shift of the axis of astigmatism through 90° and a total change of 20 dioptres. Deliberate overcorrection was followed by cautious suture removal. Definitive adjustment was delayed for six weeks, to result in a 2·00 dioptre astigmatism still in the axis of the overcorrection. Her refraction has remained remarkably stable since then. Suture removal would have been equally effective and safer if begun at eight weeks.

CASE 2 (Fig. 4)

A female aged 68 years. 10 August 1982: left intracapsular extraction (corneal section) with four-loop Binkhorst intraocular lens. 14 October 1982: −1·00 D.sp/−5·00 D.cyl axis 100°. Suture adjustment was attempted as described previously[1] but failed to improve her astigmatism, and the corneal suture was removed: −3·00 D.sp/−5·00 D.cyl axis 90°. 18 January 1983: sutures were placed in the cornea (Fig. 4) with a resulting axis shift through 90°: −5·00 D.sp/−2·00 D.cyl axis 180°=6/6.

Two weeks later the cornea was spherical and no suture removal was indicated. Four months later her refraction was still satisfactory: −4·50 D.sp/−2·00 D.cyl axis 95°=6/5. 7 July 1983: six months after suturing had been undertaken a doctor unaware of our intention of long-term retention removed all the sutures. Fortunately in this case there was only a small change, and on 13 October 1983: −4·50 D.sp/−2·50 D.cyl axis 97°=6/6 was found on refraction.

COMMENT

Overcorrection in this patient was small, and suture removal at six months carried a risk of recurrence of the original excessive error. However, the cornea in this case seems to have reached a stable form, and suture removal was not as unfortunate as expected. There is still a general misconception that corneal sutures need to be removed. It is emphasised that a

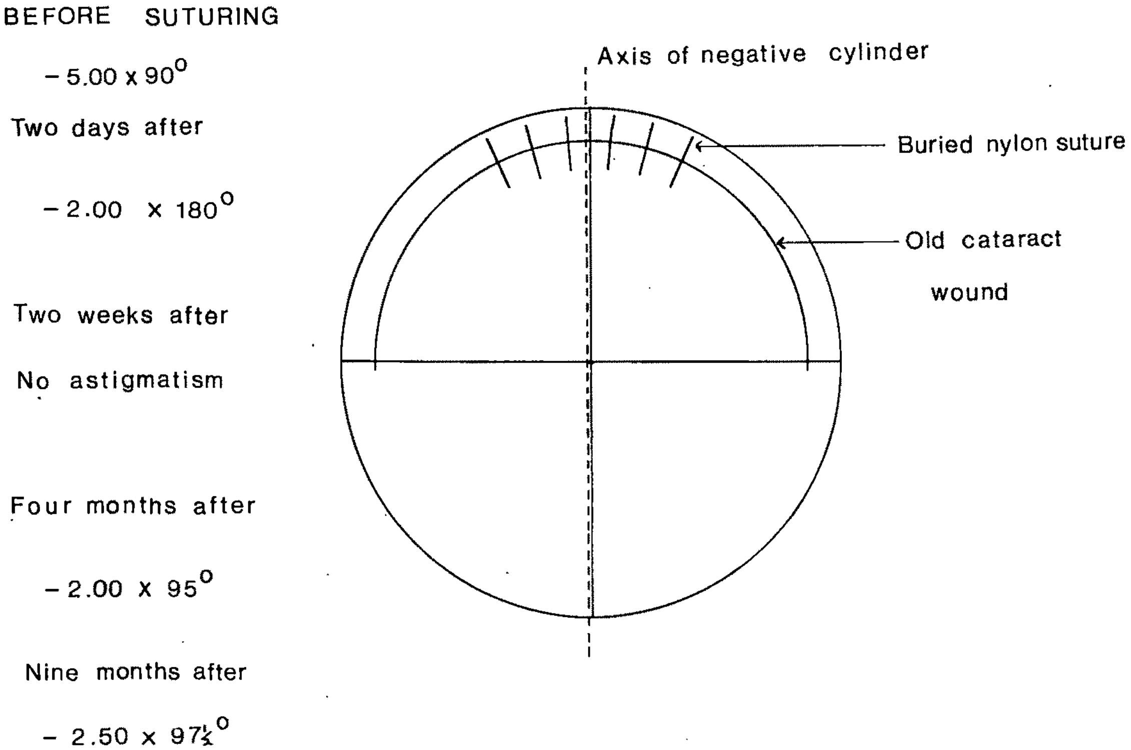

Fig. 4 *Case 2. A female aged 68 years, had astigmatism following cataract extraction with insertion of intraocular lens. The astigmatism failed to respond to adjustment of the corneal continuous suture (see text) and the suture was removed. Interrupted nylon sutures were placed around the negative cylinder axis as shown, moving the axis through 90°. Two weeks later the cornea was spherical. Four months later the cylinder was −2·00×95°. Nine months after suturing the cylinder was −2·50×97½°—that is, minimal change despite early removal of sutures (see text).*

tightly organised follow-up is needed by those who are aware of the procedure and what it is intended to achieve.

CASE 3 (Fig. 5)

A male aged 65 years. 15 November 1977: right intracapsular extraction (corneal section) with four-loop Binkhorst intraocular lens insertion. 15 February 1978: +4·00 D.sp/−7·50 D.cyl axis 75° (adjustment and suture removal had failed). 25 February 1978: suturing of cornea (Fig. 5) in the axis of the negative cylinder. Initial overcorrection to +3·50 D.sp/−6·50 D.cyl axis 130°.

After single suture removal on 17 March 1978 his refraction was +1·50 D.sp/−3·00 D.cyl axis 105°. 21 March 1983: five years later (with frequent checks over the years showing stability) his refraction was still +1·50 D.sp/−3·00 D.cyl axis 97°=6/5.

COMMENT

Initial overcorrection was adjusted after three weeks with a satisfactory long-term result. We would wait longer now before adjusting.

CASE 4 (Fig. 6)

A male aged 70 years. 30 July 1982: right intracapsular extraction (corneal section) with four-loop Binkhorst intraocular lens insertion. 30 September 1982: continuous suture adjustment for 3·50 dioptres of astigmatism was attempted, but the suture broke and was removed. Immediate refraction was −5·00 D.sp/−1·00 D.cyl axis 90°. Three weeks later on 21 October 1982: +1·00 D.sp/−7·00 D.cyl axis 70°. A row of sutures (Fig. 6) was placed round the axis of the negative cylinder giving an initial result on 28 October 1982: +0·75 D.sp/−0·50 D.cyl axis 60°. Four weeks later on 25 November 1982: −1·75 D.sp/−1·25 D.cyl axis 90°. In December 1982 he died from a severe cerebrovascular accident.

COMMENT

This amount of corneal moulding (6 dioptres) after suture removal eight weeks after operation is unusual in our experience.

This man's tragic death prevented longer follow-up, but his case demonstrates slight undercorrection of the astigmatism—less reliable than initial overcorrection.

CASE 5 (Figs. 7 and 8)

A male aged 45 years sustained a perforating injury to his right eye in June 1978. The resultant cataract

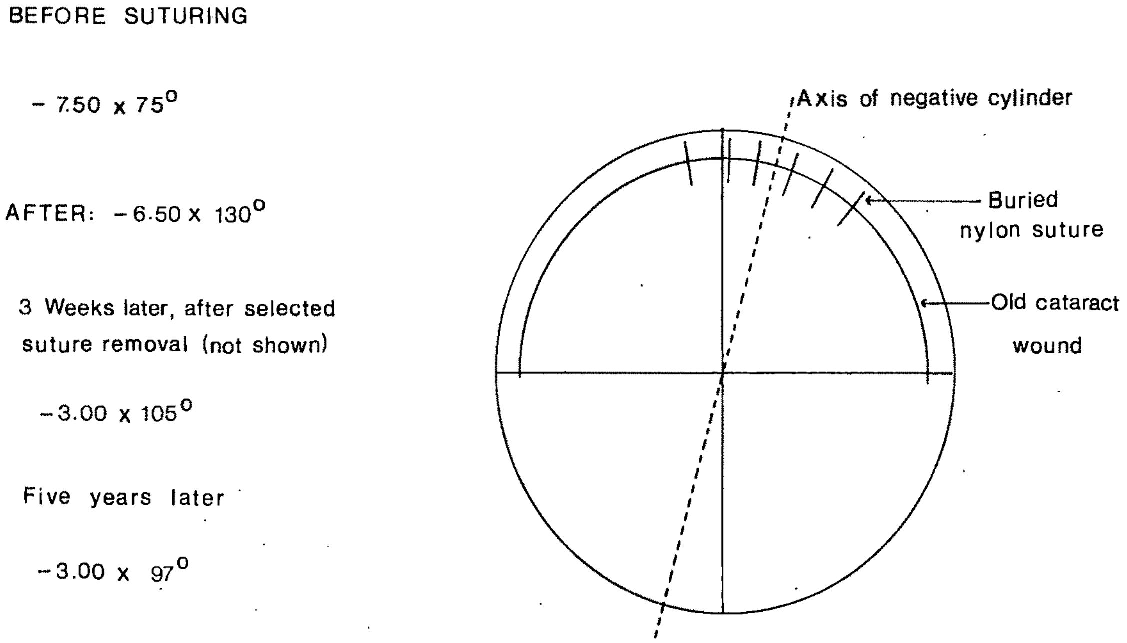

Fig. 5 *Case 3. A male aged 65 years, had astigmatism following cataract extraction and intraocular lens insertion. Suture adjustment failed (see text) and the corneal sutures were removed, following which he still had 6·50 dioptres astigmatism. Buried nylon sutures were placed around the negative cylinder axis as shown, resulting in an axis shift from 75° to 130°. Three weeks later selected sutures were removed in stages until astigmatism was only 3·00 dioptres. Five years later he retained a refraction of −3·00×97° 6/5.*

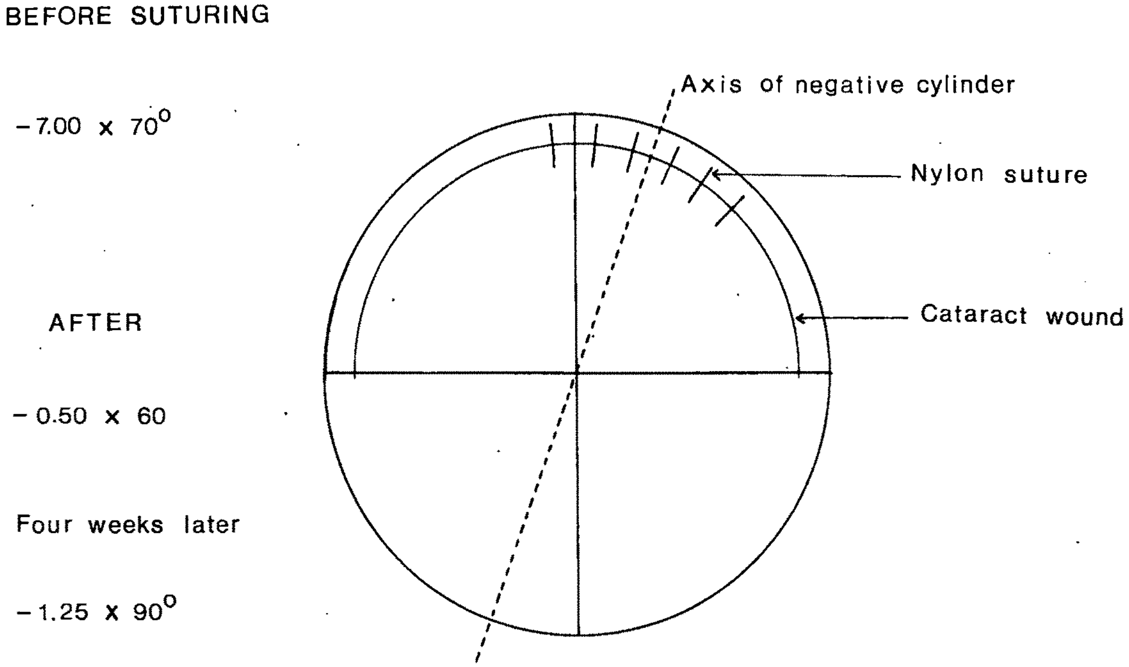

Fig. 6 *Case 4. A male aged 70 years, developed astigmatism following cataract extraction using a continuous corneal suture. Suture adjustment was attempted at eight weeks after operation, but the suture broke. Over the next three weeks the cylinder increased to −7·00×70°. Interrupted sutures were placed around the negative cylinder axis, and after one week the cylinder was −0·50×60°. A month later, eight weeks after suturing, the cylinder was −1·25×90°. Further follow-up was prevented by his death from a cerebrovascular accident.*

was removed in September 1981, but he had high astigmatism from the original scarring. 5 October 1982: +15·00 D.sp/−7·00 D.cyl axis 85°. His cornea was sutured with buried 10/0 nylon around the negative cylinder axis (Fig. 4). Subsequent refraction was +14·00 D.sp/−5·00 D.cyl axis 160°, a significant axis shift.

4 November 1982: interrupted sutures were removed in the axis of the new positive cylinder (Fig. 5) with an encouraging initial result: +15·00 D.sp/ −2.00 D.cyl axis 90°. 6 January 1983: his refraction had unfortunately changed to +17·00 D.sp/−7·00 D.cyl axis 80°.

14 April 1983: the cornea was resutured in the same manner as before. Next day: +17·00 D.sp/ −7·00 D.cyl axis 165°. One suture was removed: +15·00 D.sp/−6·00 D.cyl axis 120°. 9 June 1983: +15·00 D.sp/−5·00 D.cyl axis 110°; he had reverted to his original astigmatism.

COMMENT

The failure of both attempts at correction was probably explained by the large traumatic scar, which was more difficult to mould than keratoplasty or cataract sections. In addition the 10/0 suture material was too weak and the sutures were removed too early after both attempts. 9/0 Material is preferable.

Discussion

These suturing procedures were uncomplicated both at the time of surgery and afterwards. The procedure is simple enough to require minimal skill, provided an operating microscope is used and the sutures are placed with care. It is perhaps less easy to decide where the sutures should be placed, how many, and when they should be removed to obtain the desired long-term result. The case reports show that changes continue for some time, and it is important to exercise patience before making the definitive 'final' adjustment. The procedure is essentially reversible, and it is intended that some sutures are left in place until they degrade and fragment some two years later. By that time it seems that the refraction will have stabilised without the suture support. In case 5 a number of factors contributed to this one failure: (1) the suture used was too thin; (2) sutures were removed too early; (3) the astigmatism was due to

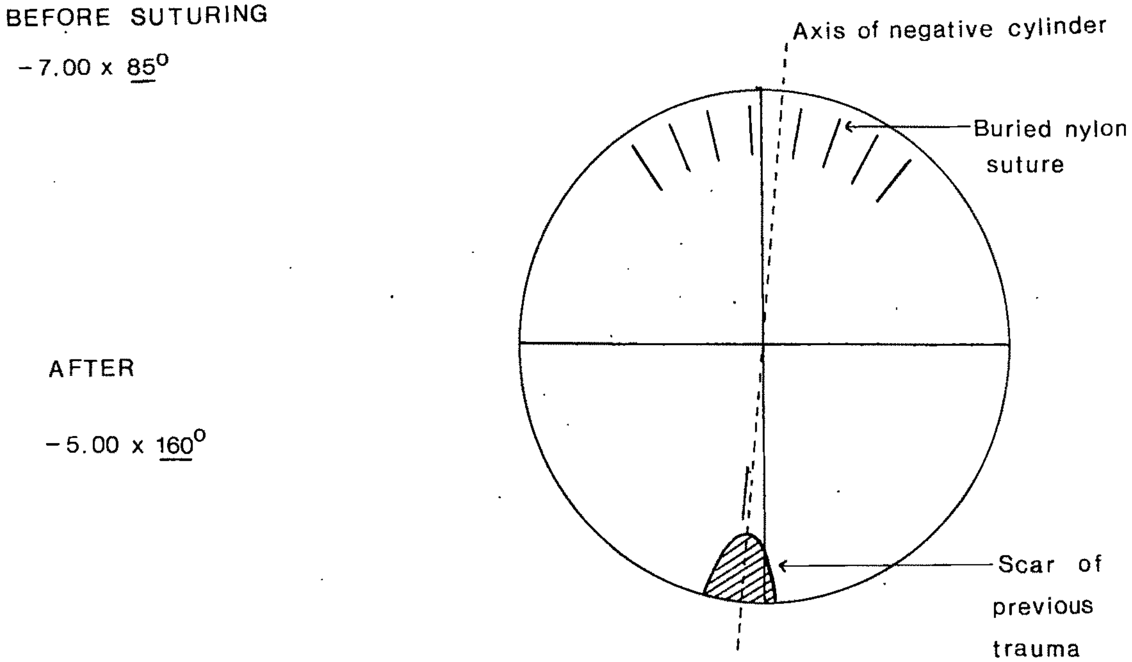

Fig. 7 *Case 5. A man aged 45 years, sustained a perforating injury with lens damage in June 1979. His lens was removed in September 1981, but astigmatism of 7·00 dioptres remained after 28 months despite removal of corneal sutures in cataract section. A row of buried 10/0 nylon sutures were placed around 85° (the negative axis) overcorrecting the astigmatism to −5·00×160°.*

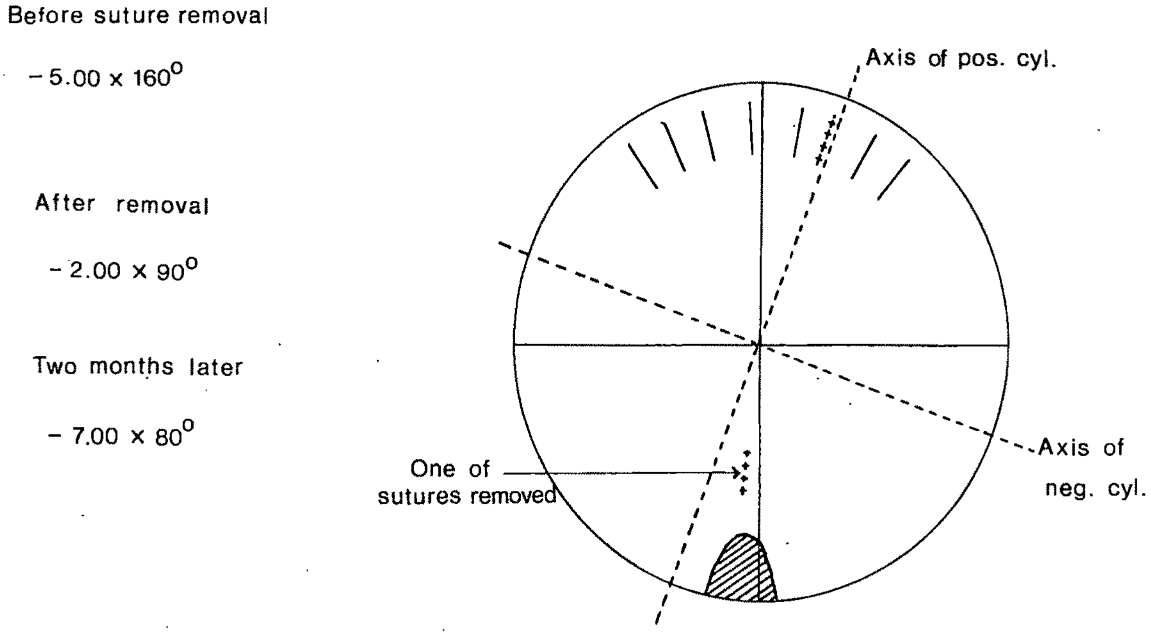

Fig. 8 *Case 5. The new negative and positive axes are shown. One week after suturing, two sutures, shown dashed, were removed, giving an initial encouraging result of 2 dioptres. However, the suture material was too weak and the sutures were removed too early. Two months later the astigmatism was back to −7·00×80°. A further attempt at suturing was also unsuccessful (see text).*

trauma and subsequent reparative surgery, resulting in two corneal wounds with complex stresses. The cornea was probably less able to undergo corneal moulding than the other cases which were routine keratoplasty or cataract sections.

From our experience of the cases described above and others in which selected suture removal or adjustment can not be applied we recommend over-correction of the astigmatism by suturing in uncut cornea with 9/0 nylon in the negative cylinder axis. After waiting 4–8 weeks for corneal moulding one selected suture is removed at a time in the new positive axis and the refractive error rechecked. 2–3 Dioptres should be left in the new axis to allow for further decay.

References

1 Roper-Hall MJ. The control of astigmatism after surgery and trauma: *Br J Ophthalmol* 1982; **66:** 556–9.

2 Fyodorov S. Surgical correction of myopia and astigmatism. In: Schachar RA, Levy NS, Schachar L, eds. *Keratorefraction.* Proceedings of the Keratorefractive Society. Denison, Texas, PO Box 145, 1980: 141–72.

3 Troutman RC. Microsurgical control of corneal astigmatism in cataract and keratoplasty. *Trans Am Acad Ophthalmol Otolaryngol* 1973; **77:** 563–72.

4 Atkins AD, Roper-Hall MJ. Control of postoperative astigmatism. *Br J Ophthalmol* 1985; **69:** 348–51.

British Journal of Ophthalmology, 1985, **69**, 360–363

Comparison between the complications of cataract surgery following local anaesthesia with short stay and general anaesthesia with a five-day hospitalisation

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SUMMARY In December 1979 97 patients underwent intracapsular cataract extraction under local anaesthetic with planned discharge on the day after operation. Twenty-three of these patients had a prolonged stay in hospital, and five of these required early operative intervention following surgical complications. Sixteen patients did not attain a visual acuity better than 6/18. The visual outcome and postoperative course are compared with those of a similar group of patients who stayed in hospital for five days after intracapsular cataract extraction.

During the summer of 1979 waiting lists for cataract surgery at the Oxford Eye Hospital steadily lengthened. In response 97 patients underwent intracapsular cataract extraction under local anaesthesia in a nine-day 'cataract drive.' Patients were selected carefully from the waiting lists after attending a screening clinic where they were examined by a senior registrar and interviewed by a social worker experienced in visual rehabilitation. This was to assess their suitability for surgery under local anaesthesia and to plan provisions for a return to the community on the day following surgery.

The aim of this retrospective study is to assess the results of this short-stay surgery in terms of the visual outcome and the complications arising as a result of the surgery combined with early discharge from hospital.

The results of the cataract drive are compared with those of a similar series of patients who had intracapsular surgery under general anaesthesia with a five-day postoperative stay in hospital. This group of patients are taken consecutively from an on-going 'cataract management study' and will be referred to as CMS patients.

Materials and methods

Patients considered suitable for the cataract drive at the screening clinic were given a date for admission to hospital between 2 and 12 December 1979. The operation was performed on the day following admission, patients being prepared for theatre in the routine manner practised in Oxford. All surgery was performed by surgeons of consultant or senior registrar status with a senior house officer or registrar as assistant. Retrobulbar and facial anaesthesia was employed in all cases, the choice of agent being left to the surgeon. All extractions were planned intracapsular and were performed with the cryoprobe with the use of Zonulysin (chymotrypsin) at the surgeon's discretion. Limbal wounds were sutured with 8/0 virgin silk and antibiotic drops or ointment applied before padding the eye.

First dressings were performed on the morning after operation by the surgeon, all eyes being examined at the bedside. If the cornea was not seen to be clear, the patients were also examined at the slit-lamp, where the intraocular pressure was measured with the Goldmann tonometer.

Patients were discharged home or to prearranged convalescence on the first postoperative day with a mydriatic and steroid/antibiotic drops, unless discharge was considered unwise by the surgeon. (A small hyphaema or a moderate rise in intraocular pressure to less than 30 mmHg was not considered reason enough to delay discharge.)

Patients were assessed in the outpatient clinic on the fourth postoperative day and refraction was performed six weeks later for spectacles.

Patients on the CMS had similar surgery under general anaesthesia with the use of 10/0 monofilament nylon sutures in place of 8/0 virgin silk.

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Gentamicin 20 mg was given subconjunctivally in place of the antibiotic drops or ointment at the close of surgery and all patients were discharged on the fifth postoperative day.

All material used for this study was obtained by the first author from scrutiny of patients' notes four years after surgery for the cataract drive and between two and four years for the CMS patients.

Results

Table 1 shows the numbers of patients in each group by age, and Table 2 shows the last recorded corrected visual acuity. Follow-up in both groups ranged from 2 to 48 months, with a mean of 19·5 months for the cataract drive and 26 months for the CMS patients. Table 3 shows the causes of decreased acuity in the eyes whose last recorded acuity was <6/18 in each group. Table 4 indicates the range of postoperative astigmatism at the six-week refraction in the two groups.

Table 5 records the surgical complications for the two groups. Of the six cases in the cataract drive with vitreous loss at surgery, chymotrypsin was used in all but one case; it was used in all the cases which suffered vitreous loss in the CMS group.

Nineteen cataract drive patients stayed in hospital longer than planned. Sixteen of these prolonged stays were due to unforeseen surgical complications (see Table 5). The other three reasons for delayed discharges were recorded as 'patient unwell,' 'patient's age,' and 'ocular pain requiring analgesia.' Four patients were readmitted with severe complications at the outpatient visit on the fourth postoperative day, making a total of 23 cataract drive patients who had an unplanned prolonged stay in hospital. Five of these had to return to the operating theatre for further surgery (two wound leaks resutured, one iris prolapse rectified, one anterior vitrectomy for pupil block glaucoma, and one vitrectomy for endophthalmitis). Of these five patients three were under the age of 65 ($0{\cdot}01<p<0{\cdot}001$). None of the 97 CMS patients required further surgery in the immediate postoperative period ($0{\cdot}05<p<0{\cdot}02$)..

Discussion

The two groups of patients reviewed were similar in age and were both selected because of the absence of other ocular pathology. Both groups had surgery performed by consultants and senior registrars skilled in a standard operation. The two major

Table 1 *Age distribution of patients*

Age	*Cataract drive*	*CMS*
45–49	1	0
50–54	5	1
55–59	7	6
60–64	10	9
65–69	17	21
70–74	19	26
75–79	18	20
80–84	12	11
85–89	6	3
90–94	2	0
Total	97	97

Table 2 *Visual acuity at last follow-up visit*

Acuity	*Cataract drive*	*CMS*
6/4–6/6	50	51
6/9	17	34
6/12	10	6
6/18	6	3
6/24	4	1
6/36	3	1
6/60	1	0
Counting fingers	0	0
Hand movements	2	1
Not recorded	4	0
Total	97	97

Table 3 *Cause for a final acuity of <6/18*

	Cataract drive	*CMS*
Surgical		
Cystoid macular oedema	2 (vitreous loss)	3 (no vitreous loss)
Corneal decompensation following capsule rupture	1	0
Pupil block glaucoma	1	0
Capsule remnants	0	1
Non-surgical		
Senile macular disease	4	1
Myopic retinal degeneration	2	0
Diabetic maculopathy	2	0
Chronic simple glaucoma (known to exist prior to surgery)	2	0
Macular hole	1	0
Tobacco/alcohol amblyopia	0	1
No cause recorded in notes	1	0
Total	16	6

Table 4 *Postoperative astigmatism at six weeks*

Astigmatism in dioptres	*Cataract drive*	*CMS*
0–1·00	30	52
1·25–2·00	36	33
2·25–3·00	14	11
3·25–4·00	7	1
4·25–5·00	4	0
Not recorded	6	0
Total	97	97

Table 5 *Surgical complications*

	Cataract drive	*CMS*
Intraoperative		
Capsule rupture	6	6
Vitreous loss	6	4
Apparent at first dressing		
IOP 25 mmHg	11(8)*	9
Macroscopic hyphaema	22(4)	8
Iris prolapse	1(1)	0
Flat anterior chamber from wound leakage	2(2)	0
Severe uveitis	1(1)	0
Occurred between 2nd and 4th postoperative days		
Pupil block glaucoma	1(1)	0
Endophthalmitis	1(1)	1
Total hyphaema	1(1)	0
Subconjunctival abscess	1(1)	0
Occurred much later		
Retinal detachment	2	1
Updrawn pupil	0	1
Total	55(20)	30

(Numbers in brackets indicate cases with prolonged hospitalisation.)

variables were the use of local anaesthesia in one group compared with general anaesthesia in the other and the difference in duration of stay in hospital.

There were more patients in the CMS group with better postoperative acuity (Table 2), but this could be accounted for by the fact that in that group visual acuity was a point of observation in a prospective study, and the best corrected acuity was always obtained at each visit. The performance of an operation is not expected to be different whatever the duration of stay in hospital, and it is as expected that the intraoperative complications were similar for the two groups (Table 5). The greater number of complications on the first postoperative day in the cataract drive patients is not explained but is not significant except for macroscopic hyphaema.

Interestingly, 9 and 11% of cases in the two groups respectively had a raised intraocular pressure to >25 mmHg, and there was a strong correlation with the use of chymotrypsin. The IOP exceeded this level in 20 of 113 cases in which it was used compared with 1 of 81 cases when it was not (p<0·001). In 8 of 11 patients in the cataract drive group the pressure was considered too high for safe discharge from hospital at the first postoperative day. Chymotrypsin should probably not be used routinely if early discharge is intended.

It has been argued[1] that there is no benefit from admission to hospital for cataract surgery in terms of patient satisfaction or the prevention of surgical complications. Only a randomised control trial will provide an answer to these contentions.

Altogether 20 of 97 patients in the short stay group were detained beyond the first postoperative day because of various complications or untoward events. That five cases required additional surgery in this group, of which three were under 65 years old, while none required it in the CMS group, is interesting. No definite conclusions as to the reason(s) for this difference can be made from a retrospective study such as this, but possibly the use of local anaesthesia for cataract extraction in patients under 65 leads to greater complications.

A major concern of short stay or day case surgery is the fear that treatable complications may not be detected quickly, and it is worrying that serious complications developed in four cases (Table 5) in the cataract drive group between the second and fourth postoperative day. This raises the question of how frequently patients should be seen after day case surgery; for, if they must be seen daily for a few days, difficulties will arise if they live outside certain limits. In the case of endophthalmitis it is commonly detected between 18 and 72 hours postoperatively,[2] and early intervention is essential for a successful outcome.[3,4] The one case in the CMS group was detected on the third postoperative day, and 6/9 vision was regained after prompt treatment.

For the cataract drive group 23·7% of patients stayed in hospital longer than was originally intended or required readmission. The criteria for readmission may become more clearly defined if day care surgery becomes commonplace, but beds must still be made available for such contingencies, and provision must therefore be made in planning and bed allocation.

If day case cataract surgery is contemplated on elderly patients, there may not be the strong social or financial incentive, as exists in some parts of the world, for patients or relatives to cope with the problems. Further, it is questionable whether patients should be discharged on the same day as they have general anaesthesia, particularly if they live alone. A further point to consider is the increasing use of intraocular implants, for which the use of general anaesthesia is even more prevalent. A discussion on intraocular lenses is outside the scope of this paper, but some principles of patient management are similar for all types of cataract surgery. It is unlikely, therefore, that day case cataract surgery will at present be suitable for all patients in Great Britain. The major difference between day case and short stay surgery is that, in the latter, the surgeon retains the option to discharge the patient and is in a position to recognise complications and detain those likely to need further treatment. Our study suggests that complications are likely to occur in the first few days postoperatively.

The aim of any surgical treatment must be to

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Presentation White, microfine, sterile ophthalmic suspension containing fluorometholone (0.1%). **Uses** Topical ophthalmic suspension for steroid responsive inflammation of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe. **Dosage and Administration** 1 to 2 drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours the dosage may be safely increased to 2 drops every hour. Care should be taken not to discontinue therapy prematurely. **Contra-indications, Warnings, etc.** CONTRA-INDICATIONS: Acute superficial herpes simplex keratitis. Fungal diseases of ocular structures. Vaccinia, varicella and most other viral diseases of the cornea and conjunctiva. Tuberculosis of the eye. Hypersensitivity to the constituents of this medication. **Warnings** Steroid medication in the treatment of herpes simplex keratitis (involving the stroma) requires great caution; frequent slit-lamp microscopy is mandatory. Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, or may aid in the establishment of secondary ocular infections from fungi or viruses liberated from ocular tissue. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with use of topical steroids. Safety and effectiveness have not been demonstrated in children of the age group two years or below. This preparation contains benzalkonium chloride and should be used with caution in association with hydrophilic contact lenses. **Use in Pregnancy** Safety of the use of topical steroids during pregnancy has not been established. **Precautions** As fungal infections of the cornea are particularly prone to develop coincidentally with long-term steroid applications, fungus invasion must be suspected in any persistent corneal ulceration where a steroid has been used or is in use. Intra-ocular pressure should be checked frequently. **Adverse Reactions** Glaucoma with optic nerve damage, visual acuity or field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens liberated from ocular tissues, perforation of the globe. Local side-effects of steroid therapy, ie skin atrophy, striae and telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Protect from freezing. **Legal Category** POM. **Package Quantities** Supplied in plastic dropper bottles of 5ml and 10ml. Basic NHS cost (as at July 1984) 5ml-£1.78, 10ml-£2.83. PL 0426/0028. Full prescribing information is available on request.

FML-NEO* PRESCRIBING INFORMATION

Presentation Sterile, white, microfine ophthalmic suspension containing fluorometholone, NF0.1% and neomycin sulpha BP0.5% (equivalent to 0.35% neomycin base). **Uses** FML NEO* is indicated for the management of steroid responsive inflam the palpebral or bulbar conjunctiva, cornea and anterior segment of the globe, when threatened or complicated by infecti neomycin-sensitive organisms. **Dosage and Administration** One or two drops in the conjunctival sac two to four times d During the initial 24 to 48 hours, the dosage may be safely increased to one drop every hour. Care should be taken not to di treatment prematurely. Shake well before using. **Contra-indications, Warnings etc.** Acute untreated purulent ocular inf Acute superficial herpes simplex (dendritic keratitis), vaccinia, varicella and most other viral diseases of the conjunctiva an Ocular tuberculosis, fungal diseases of the eye and hypersensitivity to any of the components of the drug. **Warnings** As fo above and, in addition in diseases due to micro-organisms resistant to neomycin, infection may be masked enhanced or ac the steroid. Prolonged use may result in overgrowth of nonsusceptible organisms. Articles in current medical literature in increase in the prevalence of persons sensitive to neomycin. The possibility of such a reaction should be borne in mind. If or other untoward reactions occur, discontinue the medication. **Precautions** Patients with histories of herpes simplex ke should be treated with caution. Use of topical steroids may increase intraocular pressure. Safety of intensive or protract topical steroids during pregnancy has not been substantiated. Local side effects of steroid therapy, ie skin atrophy, striae telangiectasia, are especially likely to affect facial skin. **Pharmaceutical Precautions** Shake well before using. Do not fre **Category** POM. **Package Quantities** Available in 5ml plastic dropper bottles. Basic NHS cost (as at July 1984) £1.90. PL 0426 Prescribing information is available on request.

*Trade Mark

obtain the best result with the minimum of complications at the least inconvenience to the patient. To achieve this aim in cataract surgery requires early detection of treatable complications by means of routine monitoring during the early postoperative period, with facilities to detain or readmit for further treatment if necessary.

We acknowledge the help of Mr D Boase and Dr C Buckley, who planned and organised the cataract drive.

References

1 Ingram RM, Banerjee D, Traynar MJ, Thompson RK. Day-case cataract surgery. *Br J Ophthalmol* 1983; **67:** 278–81.
2 Peyman GA. The lens, cataract and its management. In: Peyman GA, Saunders DR, Goldberg MF, eds. *Principles and practice of ophthalmology*. Philadelphia: Saunders, 1980; **1:** 599.
3 Jaffe NS. *Cataract surgery and its complications*. 2nd ed. St Louis: Mosby, 1976: 63.
4 Peyman GA, Raichand M, Bennett TO. Management of endophthalmitis with pars plana vitrectomy. *Br J Ophthalmol* 1980; **64:** 472–5.

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Retrospective study of 67 cases of secondary pars plana posterior capsulotomy

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SUMMARY A technique of late pars plana posterior capsulotomy following extracapsular cataract extraction and posterior chamber lens implantation is described. The results and complications of 67 cases with an average follow-up period of approximately 14 months are reported. The incidence of cystoid macular oedema following this procedure was 2·9%, with no incidence of retinal detachment. The procedure appears to be an acceptable method of treating a thickened posterior capsule, and in the absence of a neodymium YAG laser and in a small unit it could prove to be a reasonable substitute.

Extracapsular cataract extraction (first described by Jacques Daviel in 1753) combined with posterior chamber intraocular lens implantation is enjoying a resurgence of interest because of the reported reduction in the incidence of postoperative cystoid macular oedema and aphakic retinal detachment.[1 2] The after cataract, which forms in the scaffolding of the posterior capsule, remnants of the anterior capsule, and lens matter, presents a special problem of management in the presence of a posterior chamber lens.

This paper reports on the pars plana approach to late posterior capsulotomy, which is performed in our unit as an outpatient procedure. The complications related to this procedure are recorded.

Materials and methods

TECHNIQUE

Secondary pars plana capsulotomy was described by Lindstrom and Harris[3] and has been performed by Epstein in South Africa for many years.

In our department this procedure is performed on an outpatient basis with an operating microscope under local anaesthetic. A fine, sharp, self-sealing discission knife is essential to enable penetration of the sclera with minimal pressure. One of the authors (J.L.P.) has designed a micro needle knife for the procedure.

Anaesthesia is achieved by the following method: facial akinesia with 2% lignocaine plus 1/10 000 adrenaline by Van Lint's method, and then a small bleb of the same local anaesthetic is lifted in the inferotemporal and superonasal quadrant of the bulbar conjunctiva. The superonasal anaesthetic is necessary to enable the surgeon to grip the globe with toothed forceps. An operating microscope is used with full sterile procedure. Full pupillary dilatation is effected by topical cyclopentolate 1% and/or phenylephrine 10%. Eyelid retraction is with a Barraquer speculum, and corneal clarity is maintained with balanced salt solution (BSS) irrigation. Conjunctiva and Tenon's capsule are gripped in the superonasal quadrant, and the sclera is penetrated by the needle knife 3·75 mm from the limbus in the inferotemporal quadrant, with the initial penetration perpendicular to the sclera. The needle knife point is located in the pupil and engages the posterior capsule from below or above, and a slit is cut in such a way that it does not extend beyond the optic area of the intraocular lens.

At the end of the operation injections below Tenon's capsule of antibiotics and long-acting steroids are routinely prescribed. Patients are reexamined one hour postoperatively on a slit-lamp biomicroscope and discharged home on topical steroids and mydriatics.

PATIENTS' RECORDS

The records of 77 patients who had undergone extracapsular cataract extraction by one of the authors (J.L.P.) and subsequent pars plana posterior capsulotomy with a minimum six-month follow up (mean 14 months) were reviewed. Of these patients

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58 attended for detailed examination for the purposes of this study.

Records of all cases were studied. Their visual acuities were measured at 6 m on a Snellen's chart, refraction was performed in cases with visual acuity less than 6/6, slit-lamp biomicroscopy was performed, contact lens, three-mirror funduscopy, and indirect ophthalmoscopy were routinely performed, and fluorescein angiography was carried out on those with clinically equivocal macular disease.

Results

Fifty-eight patients (64 eyes) were included in this study (six bilateral cases), and three of them had a second procedure performed (total of 67 cases). The age range of the patients was 18–90 years (average 67). Table 1 shows the age distribution and Table 2 shows the type of cataract.

Table 1 *Age distribution of 58 patients in study*

Age group	*Number*
10–19	1
20–29	1
30–39	1
40–49	3
50–59	7
60–69	15
70–79	20
80–90	10
Total	58

Table 2 *Type of cataract in 64 eyes in study*

Type of cataract	*Number*
Senile	49
Familial	5
Traumatic	4
Congenital	2
Usher's syndrome	2
Retinitis pigmentosa	1
Complicated	1
Total	64

Table 3 *Type of intraocular lens implanted*

Type of intraocular lens	*Number*
Pearce tripod posterior chamber lens	47
Pearce Y loop posterior chamber lens	7
Binkhorst 4 loop iris clip lens	2
Boberg-Ans iris clip lens	1
Simco anterior chamber lens	1
Choyce anterior chamber lens	1
Others	1
No intraocular implant	4
Total	64

All but one of the patients underwent this procedure because of an opaque posterior capsule. The one exception had uniocular diplopia, which was eliminated by capsulotomy. The average follow-up period was 14 months (minimum six months and maximum 54 months).

Sixty of the 64 eyes had intraocular implants. Table 3 shows the type of intraocular lens implanted. Two of the 64 eyes had primary posterior capsulotomy at the time of cataract extraction. The time period between cataract extraction and late pars plana capsulotomy varied from eight months to 68 months (average 30 months).

The precapsulotomy visual acuity is shown in Table 4. The postcapsulotomy corrected visual acuity achieved at the time of the survey is shown in Table 5. Table 6 shows the causes of a corrected

Table 4 *Visual acuity before pars plana posterior capsulotomy*

Precapsulotomy visual acuity		*Percentage*
6/6 or better*	(one case)	1·5
6/12 or better		15·5
6/24 or better		36·5
Less than 6/24		46·5

*This case had uniocular diplopia due to capsular wrinkling, which was eliminated with capsulotomy.

Table 5 *Visual acuity after pars plana posterior capsulotomy*

Corrected visual acuity achieved at the time of survey (no exclusion)	*Percentage*	
6/6 or better	37·5	=75
6/12 or better	37·5	
6/24 or better	11·0	
Less than 6/24	14·0	

Table 6 *Causes of low visual acuity*

Causes of a corrected visual acuity less than 6/9	*Number*
Amblyopia	4
Cystoid macular oedema	2
Diabetic retinopathy	4
Low grade uveitis	1
Myopic degeneration	2
Optic atrophy	2.
Pigment deposit on intraocular lens	1
Retinal branch vein occlusion	2
Retinitis pigmentosa	1
Retinal branch artery occlusion	1
Senile macular degeneration	6
Thickened posterior capsule	6
Usher's syndrome	2
Vitreous membrane	1

Table 7 *Visual acuity after pars plana posterior capsulotomy*

Corrected visual acuity achieved excluding unrelated posterior pole pathology	*Percentage*	
6/6 or better	60·50	=87
6/12 or better	26·50	
6/24 or better	10·50	
Less than 6/24	2·50	

Table 8 *Complications of pars plana posterior capsulotomy in 67 cases*

Complications	*Number*
Transient rise in IOP	7
Transient uveitis	4
Vitreous haemorrhage (cleared)	3
Displacement of intraocular lens	3
Vitreous in anterior chamber	2
Cystoid macular oedema	2
Retinal detachment/dialysis	0
Endophthalmitis	0

visual acuity of less than 6/9. The corrected visual acuity achieved apart from unrelated posterior pole pathology is shown in Table 7. Table 8 shows the complications attributable to the procedure.

Discussion

Although there is sufficient evidence that the presence of an intact posterior capsule reduces the incidence of cystoid macular oedema and rhegmatogenous retinal detachment,[1,2] controversy remains on the incidence of complications after elective primary capsulotomy at the time of cataract extraction and of late capsulotomy, which would be required in approximately one-third of extracapsular cataract extractions after three years.

With a pars plana approach to late capsulotomy discission of the posterior capsule without rupturing the anterior hyaloid face would be impossible, but the presence of a close contact and probable seal between the capsulotomy margins and the optic part of the posterior chamber lens could prevent vitreous herniation into the anterior chamber and reduce vitreoretinal complications.[3] In our experience posterior capsulotomy through the anterior segment is likely to decenter the posterior chamber lens and bring vitreous into the anterior chamber and to the wound.

The entry hole for late pars plana capsulotomy is necessarily made in the ciliary epithelium, but technical error may also cause peripheral retinal perforation or dialysis. Newly formed tissue may grow into the vitreous as a result of perforation, causing localised vitreoretinal traction. The latter effect may be reinforced by vitreous haemorrhage, however slight, that may occur at the time of operation.[4] It is mandatory to avoid contact with the pars ciliaris of the ciliary body at the time of penetration of the globe, and this complication can be reduced by making the initial incision perpendicular to the sclera. There is a risk of endophthalmitis if organisms on the conjunctival surface are carried into the vitreous cavity.

In our study two of 67 cases (2·9%) who underwent late pars plana posterior capsulotomy approximately 13 and 17 months after extracapsular cataract extraction and posterior chamber lens implantation developed cystoid macular oedema. The first patient achieved a corrected visual acuity of 6/6 immediately after capsulotomy, but this reduced subsequently to 6/18 due to cystoid macular oedema. The visual acuity in the second case was 6/60 immediately after capsulotomy because of vitreous haemorrhage and remained at this level despite the vitreous clearing, a result of florid cystoid macular oedema. We presume these two cases of cystoid macular oedema were due to capsulotomy, though the prior capsular opacity precluded a clear view of the macula preoperatively. This figure compares with 3·5% incidence of cystoid macular oedema after late posterior capsulotomy with the limbal approach reported by Livernois and Sinskey.[5]

The incidence of cystoid macular oedema following late posterior capsulotomy with the non-invasive method of neodymium YAG laser has not been fully studied yet, but indications suggest a figure of around 2% (Harris, personal communication 1984).

Of the three cases of vitreous haemorrhage all cleared completely. In one patient the visual acuity dropped to 6/60 owing to cystoid macular oedema (see above); the remaining two achieved a corrected visual acuity of 6/6 and 6/12.

There were six cases of rethickened posterior capsule and/or inadequate central gap. Their visual acuities were between 6/12 and 6/18. They may have been improved with further capsulotomies.

Except for one case of vitreous membrane formation other complications in our study were transient, and slight displacement of intraocular lenses at most requiring only marginal change of optical correction. The case of vitreous membrane formation had a secondary insertion of anterior chamber lens and late capsulotomy (separate procedures) in our department following extracapsular cataract extraction in another hospital, and we could not verify the time of vitreous veil formation.

There was no incidence of retinal detachment, and although our study does not include enough patients to draw a definitive conclusion it may suggest that delaying discission for capsular thickening may reduce retinal complications. McPherson *et al.*[6] in a study of 27 eyes with retinal detachment after extracapsular cataract extraction and late posterior capsulotomy, considered that the interval between cataract extraction and discission had a significant effect on the extent of retinal detachment and recovery of visual acuity after retinal detachment repair.

In our experience pars plana late posterior capsulotomy has proved to be a satisfactory method of dealing with a thickened posterior capsule after posterior chamber lens implantation. It provides easy access to the posterior capsule and also reduces the risk of disrupting the capsular fixation of the lens. In the absence of non-invasive but expensive instrumentation (neodymium YAG laser) this procedure could prove to be a reasonable substitute.

We thank outpatient nursing staff of the Bromsgrove General Hospital for their help in conducting the survey and Miss P Quinn and Mrs C Rawlins for their secretarial assistance.

References

1 Jaffe NS, Clayman HM, Jafee MS. Cystoid macular oedema after intracapsular and extracapsular cataract extraction with and without an intraocular lens. *J Am Acad Ophthalmol* 1982; **89:** 25–9.

2 Drews RC. The Pearce tripod posterior chamber intraocular lens, an independent analysis of Pearce's results. *J Am Intraocular Implant Soc* 1980; **6:** 259–62.

3 Lindstrom RL, Harris WS. Management of posterior capsule following posterior chamber lens implantation. *J Am Intraocular Implant Soc* 1980; **6:** 255–8.

4 Schepens CL. *Retinal detachment and allied diseases.* Philadelphia: Saunders, 1983; **1:** 54.

5 Livernois R, Sinskey RM. Complications of late capsulotomy. *J Am Intraocular Implant Soc* 1981; **7:** 242–3.

6 McPherson AR, O'Malley RE, Bravo J. Retinal detachment following late posterior capsulotomy. *Am J Ophthalmol* 1983; **95:** 593–7.

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Argon laser iridotomy

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SUMMARY Argon laser iridotomy was successfully performed on 47 out of 52 eyes of 35 patients by the continuous wave argon laser. The technique of argon laser iridotomy is described in detail. A number of complications were observed. The reasons for these are discussed, and measures for the avoidance of complications are suggested.

Argon laser iridotomy was first reported in 1973 by Khuri[1] working with rabbits, and later Abraham and Miller reported success with this technique in humans.[2] Since then several series[3–10] in which various techniques were used have been published. The reports have differed on such factors as burn duration, spot size, number of burns, use of contact lens, use of steroids, and site of treatment.

Iridotomy using the dye[11] and neodymium YAG (yttrium, aluminium, garnet) laser[12] are widely reported as being effective techniques. However, the argon laser is much more generally available, and the additional expense of the Abraham lens is small. The argon laser iridotomy shares with the other two methods the advantage that it may be performed as an outpatient procedure with consequent sparing of hospital beds and attendant social disruption.

We report a critical examination of argon laser iridotomy as performed on a group of patients who would otherwise have required a surgical peripheral iridectomy, presenting at Greenwich District Hospital and St Thomas's Hospital. A technique was devised which combined the most advantageous features of previous series, drawing most particularly on the work of Pollack.[3]

The indications for surgical iridotomy were: acute angle closure, fellow eye of acute angle closure, chronic angle closure, chronic simple glaucoma with narrow angle, and pupil block glaucoma (Table 1). Patients excluded from the study were those whose intraocular pressure could not be brought under control by medical means, who therefore underwent emergency surgery.

Table 1 *Indications for iridotomy*

Diagnosis	*Number*
Acute angle closure glaucoma	16
Fellow eye of acute angle closure glaucoma	19
Chronic angle closure glaucoma	6
Chronic simple glaucoma with narrow angle	9
Pupil block glaucoma	2

Material and methods

Fifty-two eyes of 35 patients were recruited for the study. Seven were male and 28 were female. Their ages ranged from 35 to 91 with a mean age of 71 years.

A coherent radiation 900 continuous wave argon laser was used. All iridotomies were performed by one operator (R.A.H.). If the patient was not already receiving miotics, one drop of pilocarpine 1% was administered to the eye to be treated one hour prior to operation to produce miosis. A single drop of oxybuprocaine was used to anaesthetise the cornea prior to the fitting of an Abraham lens,[2] methylcellulose being used as a lubricant. This lens is a modification of the Goldmann fundus lens. A flat glass plate is attached to its anterior surface into which an 8 mm hole has been trephined and a 66 dioptre plano convex lens inserted. The principal advantage of this lens is that it produces a convergent beam which, when focused on the iris, increases the power intensity fourfold and correspondingly diminishes the relative power intensity at the cornea and the retina. The use of a contact lens also assists in fixing the eye, keeps the lids open, and acts as a heat sink for the cornea.

The site for the iridotomy was chosen at either 10 o'clock or 2 o'clock, at the base of a crypt at the junction of the inner two-thirds with the outer third of the iris. All patients were treated in either the superonasal or superotemporal iris, with the gaze directed so as to displace the macula from the firing line. In order further to minimise the risk to the

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macula 18 out of the last 20 iridotomies were performed in the superonasal quadrant, with the treated eye in adduction, and no difficulty was encountered. The authors consider that this is the safest site for laser iridotomy. Stretch burns were applied at a distance of one or two clock hours from the proposed iridotomy site.

These burns were of 0·2 second duration with a 500 µm spot size and power of 500 milliwatts. Pilocarpine induced miosis brings about radial tension and the stretch burns produce stromal contraction and circumferential tension, so the stroma at the iridotomy site becomes thin and tense.

Laser burns were then applied to the stretched area of 0·2 second duration, 50 µm spot size and power of 1000 milliwatts in the first instance. The power was adjusted according to the response of the iris stroma. In general, blue irides required a higher power than brown irides. Accurate focusing of the laser beam was essential for maximum effect. The spot size was not varied. In some patients with dark brown irides the burn duration was reduced to 0·02 second, as this brought about less stromal charring and more effective penetration. The beam was directed at the centre of the crypt until the stroma was penetrated. This was heralded by the appearance of a plume of pigment-laden aqueous, which ascended to the top of the anterior chamber, and confirmed by a clear view of the anterior lens capsule. Further burns were applied to the stroma until a hole of 0·2 mm in diameter was formed through which the anterior capsule could be clearly seen. Transillumination of the iris is an unreliable guide to the patency of the iridotomy, since stromal fibres sufficient to stop the passage of aqueous may persist after all the pigment has been dispersed.

Care was taken not to direct the beam at the lens capsule for fear of burning the lens or the underlying retina. A few patients, particularly those with blue irides, experienced some pain with the first few iris burns, but this was not severe and did not prevent the completion of the procedure. Postoperatively all patients continued their previous medications and in addition prednisolone eyedrops 0·3% were prescribed 2-hourly for 24 hours and four times a day for the next two weeks.

Patients were reviewed in outpatients one day, one week, one month, and three months postoperatively. The acuity was measured, tonometry performed, the iridotomy was examined for size and patency and the cornea, the lens and anterior drainage angle were examined, and the anterior chamber depth measured with the Haag-Striet anterior chamber depth gauge. In addition, at three months the fundus was examined ophthalmoscopically and a provocative test was performed to assess the efficacy of the iridotomy in pharmacologically induced block. This test was a modification of the method used by Mapstone[13]: one drop of pilocarpine 2% was instilled followed by one drop of phenylephrine 10% in an attempt to induce angle closure secondary to pupil block; one hour later the intraocular pressure was measured.

Results (Table 2)

A patent iridotomy was achieved in 47 eyes. Four eyes did not receive a sufficient number of laser burns to create a patent iridotomy; this was due to the inability of these patients to remain still at the slit-lamp. Two eyes were those of a 72-year old man who was aphasic and hemiplegic, the second patient was a deaf-mute, and the third a very anxious 81-year-old woman. Of the remaining 47 eyes in which a successful iridotomy was achieved three did not become patent until one month after treatment, and three more took one week before they were patent. Two of these eyes were dark brown and four were blue. A second attempt to create a laser iridotomy at the same site was not made, because absence of pigment at the treatment site in the blue irides and charred pigment at the treatment site in the dark irides would have made further laser ineffective. Furthermore, because laser iridotomies observed over several weeks showed progressive enlargement there were grounds to expect that the closed iridotomies would open up. In a further three eyes the amount of pigment at the treatment site after one session of treatment was sufficient to justify a second session two days later, and in these cases a patent iridotomy was easily achieved.

Closure occurred in two patients. In the first case the iridotomy was only 0·05 mm in diameter and became blocked by pigment from the posterior chamber. The iridotomy was easily opened and enlarged by a second session of laser treatment. The second patient had marked anterior chamber flare

Table 2 *Results*

Number of eyes	52
Total successful	47
Technical failures	4
Iridotomy patent immediately	38
Iridotomy patent after 1 week	3
Iridotomy patent after 1 month	3
Iridotomy requiring 2 treatment sessions	3
Closure: early; re-opened	1
late due to chronic iritis	1

Iris colour	*Mean energy used (joules)*
Blue	37·0
Hazel	31·8
Light brown	28·4
Dark brown	24·0

and cells at the time of treatment. The anterior chamber activity did not subside until three weeks later, by which time the patent iridotomy had become closed. No attempt was made to reopen it with the laser.

Comparisons were made between the anterior chamber depth and gonioscopic appearance preoperatively and at three months. Deepening of the anterior chamber based on the comparison of the means of three readings made with the Haag-Streit pachymeter was observed in 24 eyes. In 10 eyes the anterior chamber became shallower and in four eyes it remained unchanged. On gonioscopy the angle became more open in 16 eyes, more closed in eight eyes, and remained the same in 20 eyes. Many patients stopped pilocarpine treatment over this time and others had their dosage changed, and so in some instances the deepening of the anterior chamber may be attributable to the reduction or cessation of pilocarpine treatment. Forty-five patients were examined ophthalmoscopically after three months and no retinal burns were seen.

Forty-one patients underwent a provocative test to induce pupil block and angle closure but none developed raised intraocular pressure.

Thirteen patients complained of pain or headache within 24 hours of operation (Table 3). In each case the pain resolved and required no stronger analgesia than aspirin.

Eight eyes lost one line of visual acuity and four eyes lost two lines. The remainder either improved or stayed the same. Where two lines of acuity were lost, this was due to enlargement of a malignant melanoma in one case, further progression of already severe nuclear sclerosis in a second case, and in two cases the acuity obtained was at all times unreliable because of the patient's inability to cooperate.

Ten eyes had small endothelial opacities at the end of the procedure. In four eyes opacities were still visible after one week but all had disappeared by one month.

Lens burns were present in 21 eyes. They were small anterior subcapsular lens opacities lying immediately posterior to the iridotomy. They were usually 0·05 mm in diameter, the largest being 0·15 mm in diameter. They did not impair vision and were not seen to enlarge during the three months of follow-up.

All eyes had some flare and pigment debris immediately after treatment. Twenty-two eyes had some anterior chamber activity after one week, but after one month occasional cells in the anterior chamber were seen in only six eyes. However, persistent anterior chamber activity and posterior synechiae were seen in one case where there was a prolonged anterior uveitis which had been present prior to treatment. Not all patients' pupils were dilated at the end of the study, and so the true incidence of posterior synechiae is not known.

Table 3 *Complications*

Pain or headache within 24 hours	13
Pigment in the angle	42
Lens opacity	21
Intraocular pressure rise within 24 hours	5
Loss of visual acuity of 2 lines or more	4
Corneal burn lasting more than one week	4
Monocular diplopia	2
Posterior synechiae	1

Eye iris colour	*Percentage developing lens opacities*
Blue	29%
Hazel	29%
Light brown	53%
Dark brown	75%

In five cases a preoperative intraocular pressure of less than 22 mmHg rose to greater than 25 mmHg 24 hours later. In only one case did the pressure rise above 30 mmHg.

Pigment in the trabecular meshwork was seen inferiorly between 5 and 7 o'clock in 42 eyes.

Two patients developed intermittent monocular diplopia. In both instances the iridotomy was large (smallest diameter 0·5 mm and 1·0 mm), and the diplopia was not troublesome.

Discussion

Laser iridotomies were successfully produced in 47 out of 48 eyes that underwent the complete procedure. In 38 out of 52 eyes a patent iridotomy was immediately produced. The overall success rate of 90% is lower than most other series,[3-6] but careful patient selection could have improved this. The number of patients successfully treated in one session is the same as one series[8] but greater than most.[3 5 6]

No difficulty was found in penetrating the iris, nor was there the high incidence of closure described in other papers,[3 5 8] and relatively few patients had more than one treatment session. Clearly those patients who did not develop a patent iridotomy until some days or weeks after operation were at risk of angle closure. However, only one of these patients had had a previous attack of angle closure and she was observed as an inpatient until the iridotomy became patent.

In the majority of cases the iridotomy enlarged over the period of follow-up. This is contrary to the experience of some authors, who report a high incidence of closure which occurred during the first six weeks after operation.[3 5 8] We consider that our low incidence of closure may be attributable to the maintenance of steroid treatment for two weeks or more, thereby diminishing anterior chamber activity and pigment epithelial proliferation. The authors reporting a high incidence of closure used steroids for three days only,[3] probably for only 36 hours,[8] and not at all.[5]

Contrary to the findings of several authors[2 3 9] we found, like Yassur *et al.*,[6] that the laser energy required to produce an iridotomy was greatest in patients with blue eyes (see Table 2). Had we not treated the dark brown irides of Negro or Asian patients with short duration burns of 0·02 second we would probably have found, like Quigley,[7] that the blue and dark brown irides required the greatest amount of treatment. The difficulty encountered in penetrating blue irides arose because the pigment epithelium and the stromal pigment were dispersed by the first few laser burns, and unless penetration was achieved before depigmentation of the stroma considerable energy was required to penetrate the translucent stroma, which absorbed laser energy very poorly.

The incidence of lens opacities in our series was high. Lens opacities are probably caused by heat conducted to the anterior capsule from adjacent pigment epithelium rather than from direct laser burns to the lens capsule.[14 15] This suggestion is supported by our finding that the incidence of lens opacities was higher in the dark coloured eyes (Table 3), where the pigment epithelium is densest, and lower in the light coloured eyes, where there is less pigment epithelium, and the risk of direct laser burns of the anterior capsule is actually greater. Lens opacities have been found not to enlarge[6 10 16] even after follow-up for as long as eight years.[17] Others have found an incidence of between 0%[4 5] and 54%.[4] It was striking that those series with the fewest lens opacities used short duration burns of 0·02 second and power of 1000 to 1500 mW. Yamanoto *et al.* compared short duration burns with long duration burns and found an incidence of lens opacities of 54% where long duration burns were used and of 3% where a burn duration of 0·02 second was used.[4]

In five of our cases a preoperative intraocular pressure of less than 22 mmHg rose to greater than 25 mmHg in the first 24 hours. Yamanoto *et al.*[4] found the same rise in intraocular pressure in 42% of their patients. This rise was maximal after the first hour, with a mean increase of 12 mmHg, and then steadily declined. It is probable that some of our patients had unrecorded elevations of intraocular pressure. In the series of Yamanoto *et al.* the administration of either timolol drops 0·5% or indomethacin drops 0·5% or retrobulbar lignocaine had no influence on the rise in intraocular pressure. We suggest that acetazolamide 250 mg four times daily should be administered for the first 24 hours after operation, the first dose being given with the preoperative miotics.

Pigment on the trabecular meshwork was seen inferiorly between 5 and 7 o'clock in 42 eyes. In one study tonography was performed after laser iridotomy[9] and showed decreased outflow facility in 89% of eyes. However, there was no measurement preoperatively and the findings might very well be attributed to pre-existing trabecular damage. At present it is not possible to say whether pigment deposition damages the trabecular meshwork or affects the outflow facility after argon laser iridotomy.

Others have reported cystoid macular oedema,[18] snuffing of the central field,[19] hyphaema, and retinal burn.[16] We did not observe any of these complications.

We have found that iris penetration can be achieved without excessive difficulty, and consider that this is a practical and safe alternative to other methods of making an iridectomy or iridotomy.

R A Harrad was the holder of a research fellowship from the Iris Fund for the Prevention of Blindness at the time this work was done. The authors thank Mrs Penny Wright for secretarial assistance.

References

1 Khuri CH. Argon laser iridectomies. *Am J Ophthalmol* 1973; **76:** 490–3.

2 Abraham RK, Miller GL. Outpatient argon laser iridectomy for angle-closure glaucoma: a two year study. *Trans Am Acad Ophthalmol Otolaryngol* 1975; **79:** 529–38.

3 Pollack IP. Use of argon laser energy to produce iridotomies. *Trans Am Ophthalmol Soc* 1979; **77:** 674–706.

4 Yamanoto T, Shirato S, Kitazawa Y. Argon laser iridotomy in angle-closure glaucoma: a comparison of two methods. *Jpn J Ophthalmol* 1982; **26:** 387–96.

5 Mandelkom RM, Mendelsohn AD, Olandev KW, Zimmerman TJ. Short exposure times in argon laser iridotomy. *Ophthalmic Surg* 1981; **12:** 805–9.

6 Yassur Y, Melamed S, Cohen S, Ben-Siva I. Laser iridotomy in closed angle glaucoma. *Arch Ophthalmol* 1979; **97:** 1920.

7 Quigley H. Long term follow-up of laser iridotomy. *Ophthalmology* 1981; **88:** 218–24.

8 Podos SM, Kels BD, Moss AP, Ritch R, Anders MD. Continuous wave argon laser iridectomy in angle-closure glaucoma. *Am J Ophthalmol* 1979; **88:** 836–42.

9 Karmon G, Vender T, Savir H. Evaluation of laser iridectomy in angle-closure glaucoma: provocative tests. *Br J Ophthalmol* 1982; **66:** 471–3.

10 Abraham RK, Miller GL. Out patient argon laser iridectomy for angle-closure glaucoma. *Adv Ophthalmol* 1977; **34:** 186–91.

11 Bass MS, Cleary CV, Perkins ES, Wheeler CB. Single treatment laser iridotomy. *Br J Ophthalmol* 1979; **63:** 29–30.

12 Frankhauser F, Lortsher H, Vander Sypen E. Clinical studies of high and low power laser radiation upon some structures of the anterior and posterior segments of the eye. *Int Ophthalmol* 1982; **5:** 15–32.

13 Mapstone R. The fellow eye. *Br J Ophthalmol* 1981; **65:** 410–3.

14 Wheeler CB. Laser iridectomy. *Phys Med Biol* 1977; **22:** 1115–35.

15 Watts GK. Argon laser irradiation of the iris. *Non-ionising Radiation* 1970; **1:** 155–8.

16 Pollack IP, Patz A. Argon laser iridotomy: an experimental and clinical study. *Ophthalmic Surg* 1976; **7:** 22–30.

17 Abraham RK. Protocol for single session argon laser iridectomy for angle-closure glaucoma. *Int Ophthalmol Clin* 1981; **21:** 145–66.

18 Choplin NT, Bene CH. Cystoid macular oedema following laser iridotomy. *Ann Ophthalmol* 1983; **15:** 172–3.

19 Balkan RJ, Zimmerman TJ, Hesse RJ, Steigner JB. Loss of central visual acuity after laser peripheral iridectomy. *Ann Ophthalmol* 1982; **14:** 721–3.

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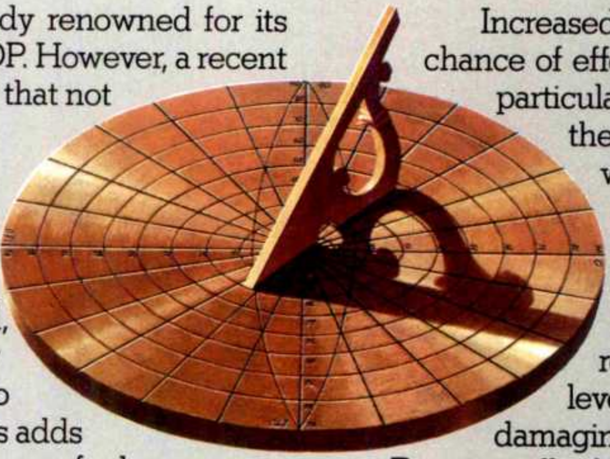

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REFERENCES
1. Sponsel, W. E., *et al., Brit. J. Ophthal.*, 1983, 67, 220.
2. Norell, S. E., *Amer. J. Ophthal.*, 1981, 92, 727.
3. MacKean, J. M., and Elkington, A. R., *Brit. J. Ophthal.*, 1983, 67, 46.
4. Reynolds, P. M., *Glaucoma*, 1982, 262.
5. Willcockson, J., and Willcockson, T., *Glaucoma*, 1982, 155.

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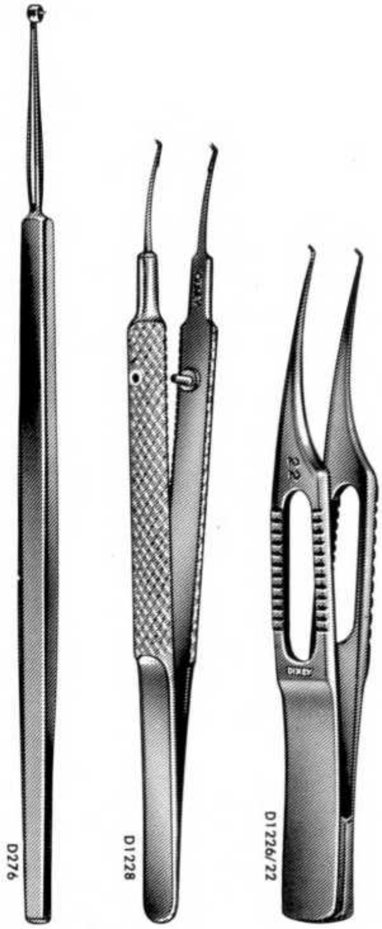

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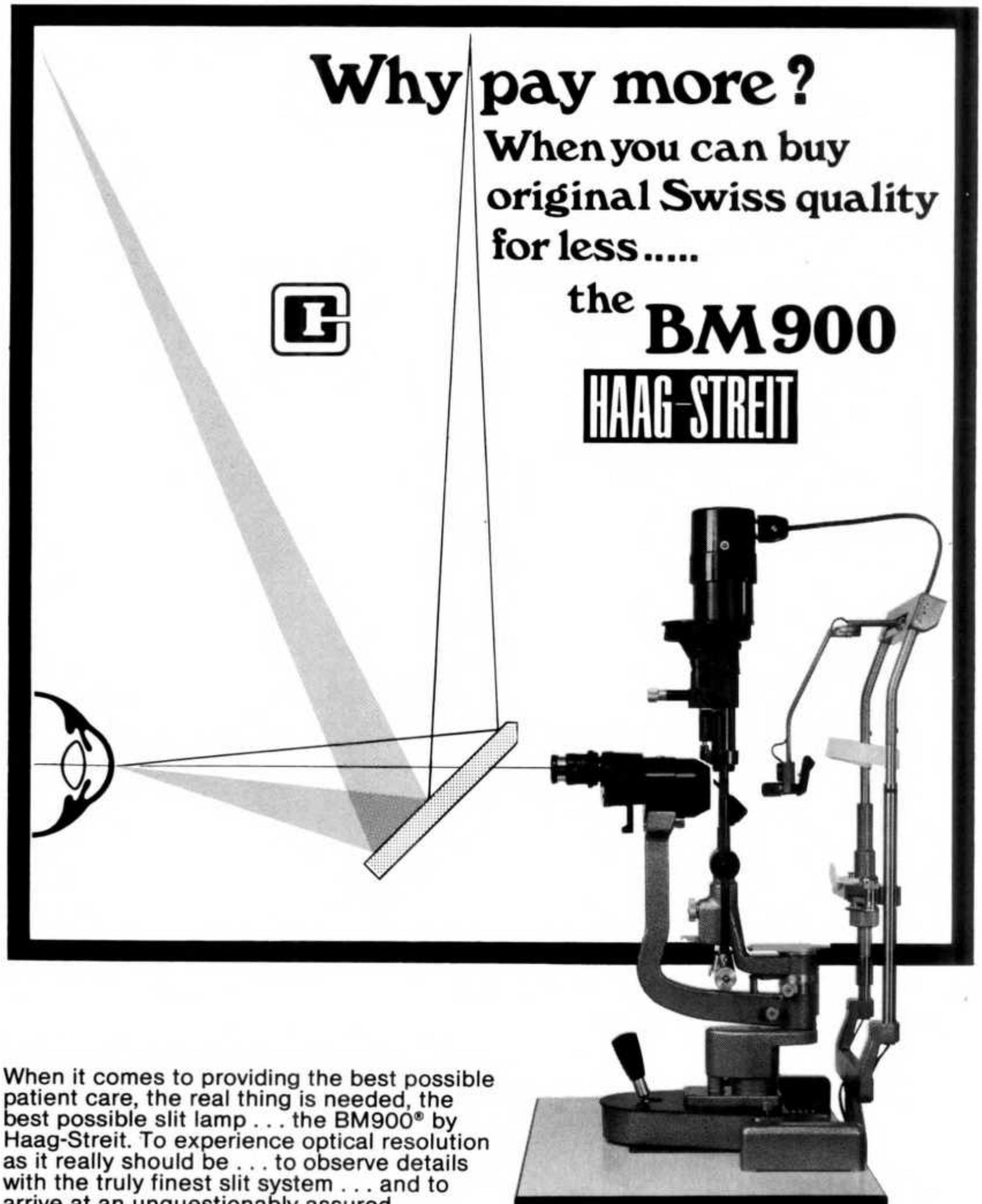

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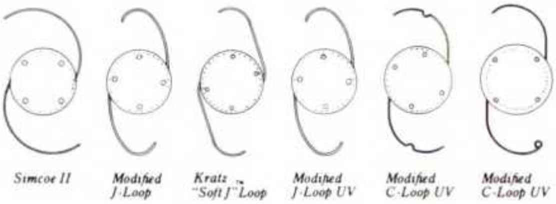

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Epithelial morphological response to soft hydrogel contact lenses

J P G BERGMANSON, C MONTAGUE RUBEN, AND L W-F CHU

From the Institute for Contact Lens Research, University of Houston, Texas, USA

SUMMARY Hydrogel (HEMA) contact lenses of increased thickness were worn by owl monkeys *(Aotus tivergatus)* under open and closed eye conditions to study ultrastructurally the corneal epithelial response to increased stress. The 0·07 mm thick lens with a calculated Dk/L of 13 had minimal effect on the epithelium, while thicker (0·2–0·4 mm) lenses with a Dk/L of 4·2–2·2 caused an epithelial thinning without oedema. This thinning was due to a loss of superficial cells and a flattening of the remaining ones. Factors in the mechanism of epithelial thinning without oedema may include anoxia, trauma, lid pressure, and lens weight. The 0·4 mm thick lens offers negligible gas transmission in the closed eye, and after 48 hours much of the epithelium was stripped, while oedema and degenerative cytoplasmic changes were prominent in areas of surviving cells. In such areas the thickness of the epithelium was reduced to one or two layers of cells. The basement membrane was in all experiments unharmed by hydrogel contact lens wear. The epithelial innervation was maintained in all corneas except those of the closed eye, and this finding correlates well with the good corneal touch threshold in soft contact lens wearers.

Although the hydrogel contact lenses have been commercially available for over a decade, reports on primate controlled studies of the ultrastructural response to such lenses are sparse.[1] There is an abundance of physiological and pathological evidence of individual variations in response as seen in the human at clinical levels of observations.[2]

The present study was designed to examine the corneal epithelial stress effects of different thicknesses of soft lenses over various time periods and to study this on the primate eye by means of the electron microscope. Furthermore, the contact lens oxygen gas flow was measured by calculation and the lens pressure effects correlated with degrees of anoxia.

The results will be compared with the recent study in the same laboratory of Bergmanson and Chu.[3] They studied primates wearing hard non-permeable corneal lenses (PMMA) for 2 to 24 hours, and their results indicated epithelial loss, atrophy and oedema.

Material and methods

Hydrogel lenses of different thicknesses (Table 1) were fitted on four owl monkeys *(Aotus tivergatus)*, while three additional owl monkeys served as control. By varying the thickness and the wearing time of the hydrogel lenses different levels of epithelial stress were achieved (Table 2). The monkeys wore similar lenses in both eyes except for the closed-eye part of the experiment, when one eye was left open and without a lens (Table 1). The contact lenses were calculated to have Dk/L values according to the formulations described by Fatt and St Helen.[4] This value is based on the material permeability (Dk) to oxygen at normal atmospheric pressure and to the thickness (L) (Table 2).

Table 1 *Experimental protocol*

Monkey	*Lens thickness*	*Wearing time (hours)*	*Lid position*
1 OD	0·07	2	Open
OS	0·07	8	Open
2 OD	0·2	15	Open
OS	0·2	15	Open
3 OD	0·4	12	Open
OS	0·4	12	Open
4 OD	0·4	48	Closed
OS	No lens		Open
5 OD	No lens Control	N/A	Open
OS			Open
6 OD	No lens Control	N/A	Open
OS			Open
7 OD	No lens Control	N/A	Open

Correspondence to Professor C M Ruben, Institute for Contact Lens Research, University of Houston, University Park, Houston, Texas 77004, USA.

Table 2 *Specification of hydrogel lenses used in the experiment*

	Material	*H_2O content*	*Thick mm(t)**	*Overall Diam. (OD)†*	*Base curve*	*Power*	*Dk/L‡*
Thin lenses	HEMA	38%	0·07	14·6	8·50	−3·00	13
Medium thick lenses	HEMA	38%	0·20	14·5	8·15 8·30	Plano to −0·50	4·5
Thick lenses	HEMA	38%	0·40	14·0	8·15 8·30	Plano to −0·50	2·2

Tolerances: *t=±0·02. †OD=±0·50. ‡Fatt and St Helen.[4]

The keratometry measurements of these animals ranged between r=7·49 mm (45·5 D) and r=6·59 mm (51·25 D), and the mean corneal diameter was 13·0 mm±0·5 mm (SD). The contact lens fittings were not tight or centrally steep, allowing a lens movement of about 1 mm on pressure, and in all cases limbal coverage was present. This fit was therefore consistent with acceptable human clinical criteria.

No sedation or topical anaesthetic was used during the experiment except in the single instance of the animal wearing a lens for 48 hours. In the last case the animal was anaesthetised with pentobarbitone (Nembutal) only for the lens insertion and surgical suturing of the lids. The closed eye was effected by cutting the inner half of the lid margin with a razor knife and using a continuous 4 'o's silk suture along the whole width of the lids completely to close the palpebral aperture. All animals were kept in an alert state while wearing the lenses.

At the end of the experimental period the animals were deeply anaesthetised and the eyes enucleated; they were then killed by a fatal dose of the anaesthetic. The enucleated eyes were immediately placed in fixative (3% glutaraldehyde in 0·2 M cacodylate buffer at pH 7·2). The central half of the cornea was dissected free and divided into sectors with the apex towards the centre. Sectors from different orientations were selected for light and electron microscope observations. The tissue thus examined amounted to approximately a quarter of the cornea.

After being poststained in 1% osmium tetroxide for 3 hours the tissues were dehydrated through an alcohol series and embedded in Epon 812. Semithin (1 μm) light microscope sections were stained in toluidine blue, while the thin sections for the electron microscope were stained firstly in 3·5% uranyl acetate and subsequently in Reynold's lead citrate. The ultrastructural observations were made with a Jeol 100C electron microscope.

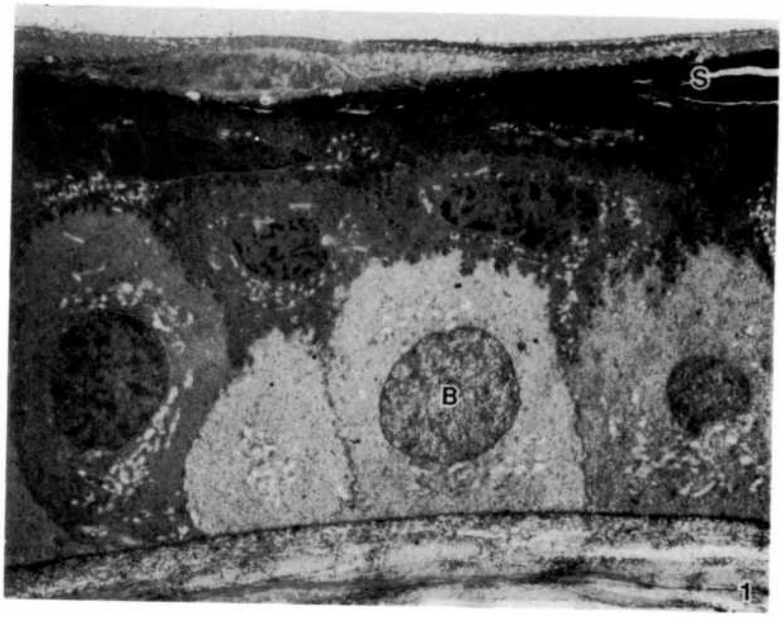

Fig. 1 *Normal epithelium of non-contact lens wearing eye. The epithelium is formed by approximately five layers of tightly packed cells. The internal basal cell* (B) *layer adheres to a basement membrane. A squamous cell* (S) *shows separation of the nuclear membranes. (Control owl monkey,* × *4380).*

Results

CONTROL EYE

Five to six layers of cells formed the epithelium. The tightly packed cells adhered to each other through numerous desmosomes, while internally the columnar basal cells were anchored by hemidesmosomes to the basement membrane, which in tranverse section was linear (Fig. 1). Squamous cells occasionally displayed cytoplasmic pallor, separation of the nuclear membranes, and partial loss of contact to adjacent cells.

MINIMAL EPITHELIAL STRESS (THIN HYDROGEL LENSES IN OPEN EYE)

One monkey wore 0·07 mm thick lenses for two and eight hours. The corneal epithelium of the eye that had worn the lens for two hours showed no morphological variation from the control. Eight hours of thin lens wear caused minimal epithelial changes, which were restricted to a small increase in atrophic cells along the surface (Fig. 2). All other cells had maintained a normal shape and cytoplasm. No spaces between cells were observed.

MODERATE EPITHELIAL STRESS (MEDIUM TO THICK HYDROGEL LENSES IN OPEN EYE)

One animal wore 0·2 mm thick lenses, while another wore 0·4 mm thick lenses. The wearing times were 15 and 12 hours respectively. All eyes showed corneal epithelial thinning, which was only marginally more advanced in the monkey wearing the 0·4 mm thick HEMA lens. In most places the epithelium was reduced to three to four cells thickness (Fig. 3). In addition to the loss of superficial cells flattening of the remaining cells accounted for part of the overall reduction in epithelial thickness (Figs. 3, 4). The surface squamous cells had generally lost their normal cytoplasmic texture. There were no further degenerative changes in the other remaining cells other than the indicated cell deformation as well as irregularities of some nuclei. The cells remained

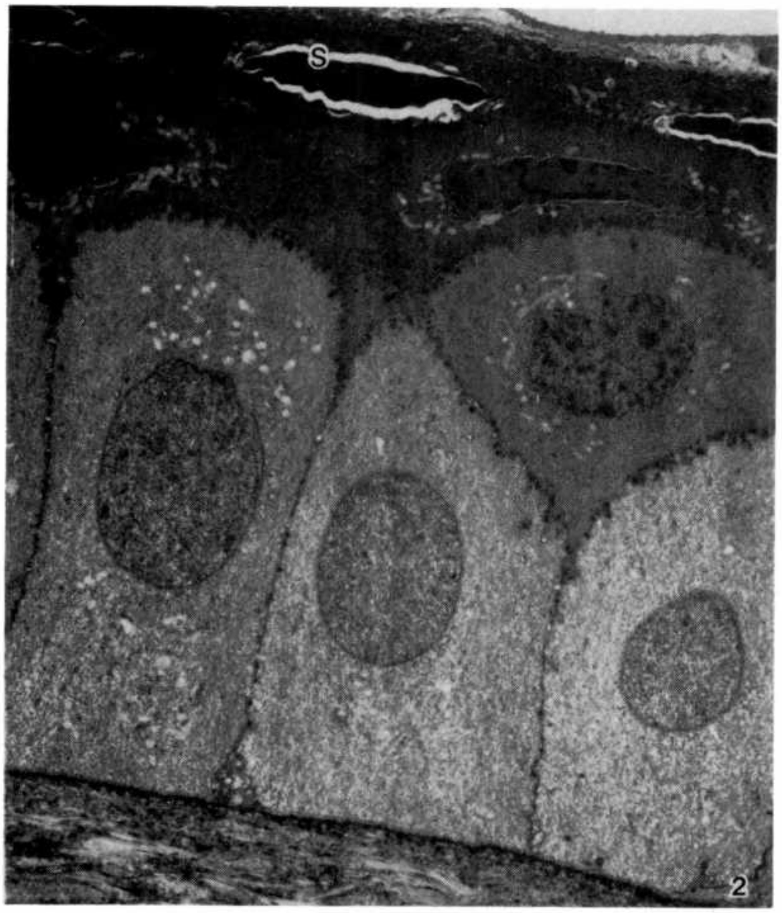

Fig. 2 *Thin contact lens wearing eye. The surface layer of cells have lost their normal texture. The nuclear membranes have separated in one squamous cell* (S). *(Owl monkey wearing of 0·07 mm thick HEMA lens for 8 hours, open eye, × 4000).*

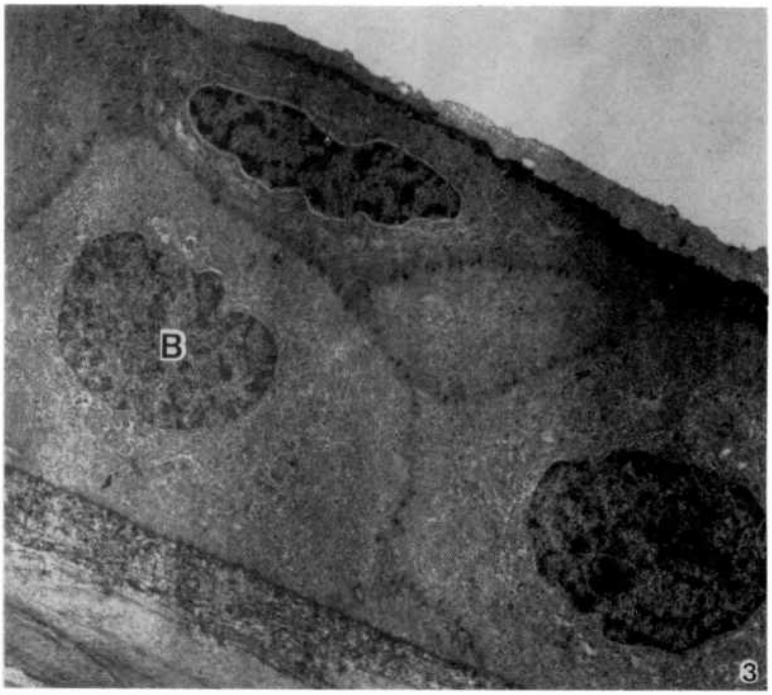

Fig. 3 *Medium thick contact lens wearing eye with thinned epithelium. The epithelium is reduced to three or four cells thickness. Flattening of especially the basal cell* (B) *layer has further reduced the overall thickness. The cytoplasm appears normal and the cells are tightly packed. (Owl monkey wearing 0·2 mm thick HEMA lens for 15 hours, open eye, × 4255).*

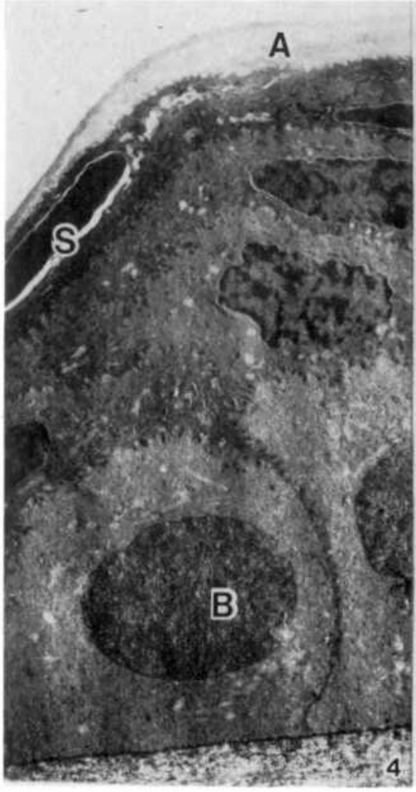

Fig. 4 *Medium thick contact lens wearing eye with transitional zone of epithelial thinning. The surface cells* (A) *have lost their normal texture while the deeper cells show a graduated flattening of the five layers of tightly packed cells. The internal basal cell* (B) *layer adheres to a basement membrane. A squamous cell* (S) *shows separation of nuclear membranes. (Owl monkey wearing 0·2 mm thick HEMA lens for 15 hours, open eye, × 3830).*

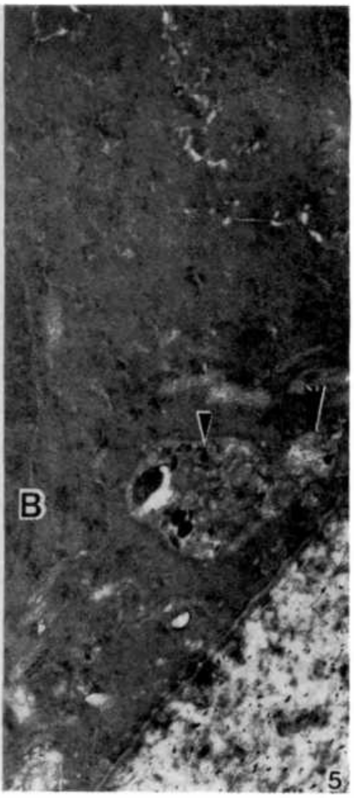

Fig. 5 *Thick contact lens wearing eye normal epithelial nerve terminal. An axon* (arrowhead) *in the internal aspect of the basal cell* (B) *layer terminates in a swelling (0·7 µm)* (triangle) *filled with mitochondria. (Owl monkey wearing a 0·4 mm thick HEMA lens for 12 hours, open eye, × 25 530).*

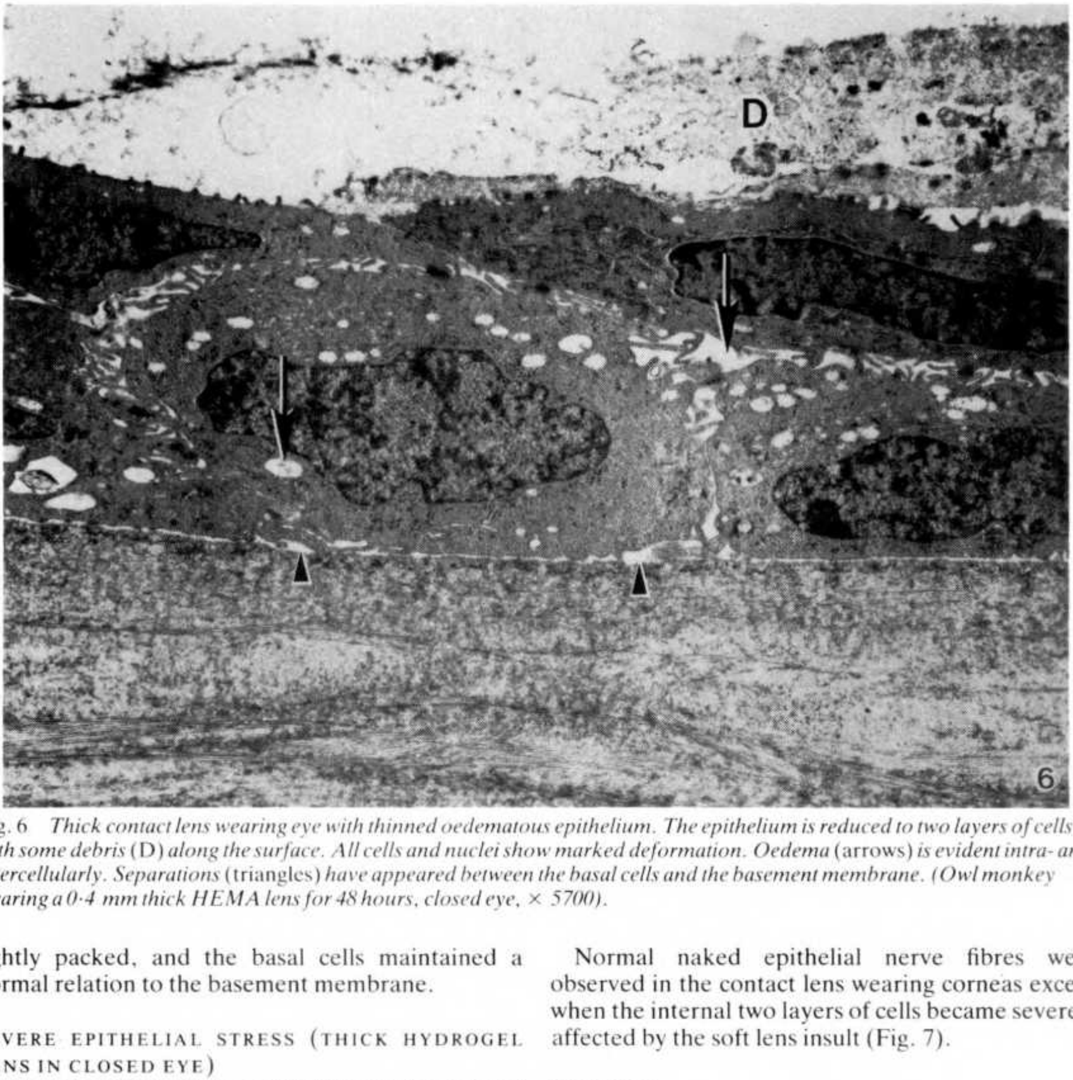

Fig. 6 *Thick contact lens wearing eye with thinned oedematous epithelium. The epithelium is reduced to two layers of cells with some debris* (D) *along the surface. All cells and nuclei show marked deformation. Oedema* (arrows) *is evident intra- and intercellularly. Separations* (triangles) *have appeared between the basal cells and the basement membrane. (Owl monkey wearing a 0·4 mm thick HEMA lens for 48 hours, closed eye,* × *5700).*

tightly packed, and the basal cells maintained a normal relation to the basement membrane.

SEVERE EPITHELIAL STRESS (THICK HYDROGEL LENS IN CLOSED EYE)

One monkey wore a 0·4 mm thick lens under sutured lids on one side for 48 hours, while the opposite eye was left open. The wearing of a thick HEMA lens under closed eye conditions stripped large areas of its corneal epithelium. In other areas marked epithelial thinning was apparent (Figs. 5, 6). The surviving cells were separated from each other by numerous small spaces. Pronounced cellular and nuclear deformation had occurred along with the formation of many intracellular spaces. The remaining basal cells had partially separated from the basement membrane. The areas of the cornea that had been denuded of its epithelium still possessed an intact and uninterrupted basement membrane. Structural changes in the underlying and anterior stromal tissue were not noticed.

Normal naked epithelial nerve fibres were observed in the contact lens wearing corneas except when the internal two layers of cells became severely affected by the soft lens insult (Fig. 7).

Discussion

The present study examines the short-term effect of hydrogel lens wear on a primate cornea, which closely resembles the human cornea.[5 6] Although the experiment involved relatively few animals, the findings were consistent and therefore allowed analogies with the human situation.

The trauma from a contact lens may be due to mechanical pressure, negative suction, abrasion from lens movement, or abnormal metabolism. The present study used the same contact lens material in all fittings, and therefore the thickness variants will determine the degree of hypoxia as well as the pressure at the corneal lens interface. Disturbance of the cell organelles would be indicative of oxygen

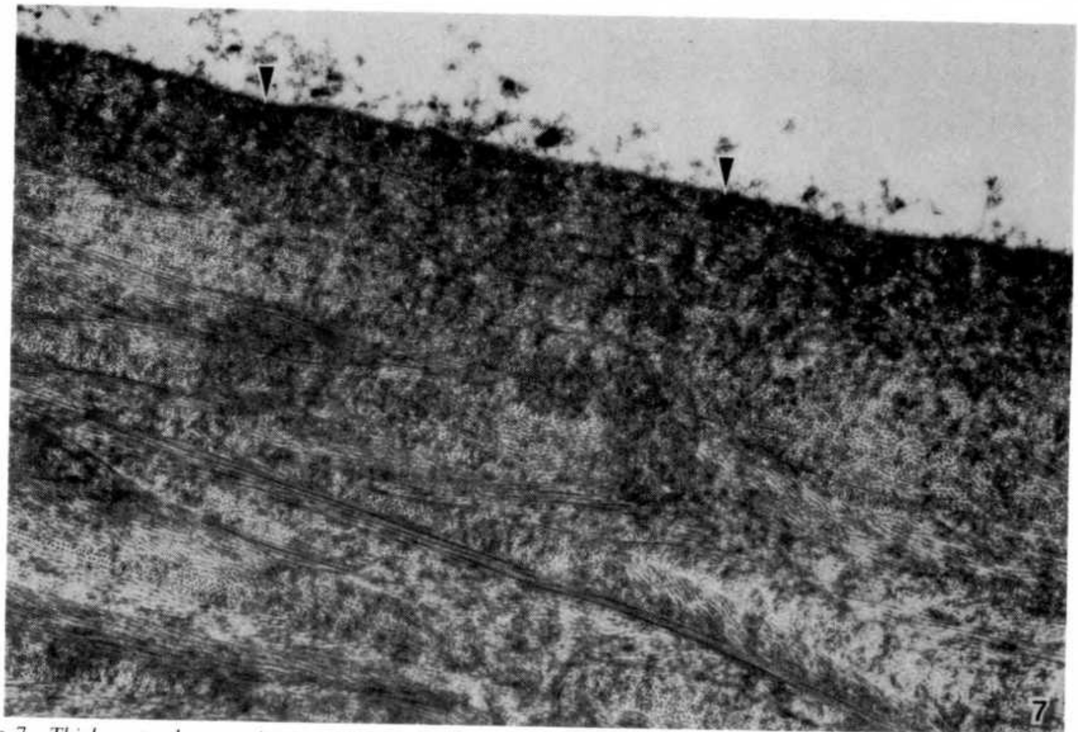

Fig. 7 *Thick contact lens wearing eye with epithelial denudation. In the areas of epithelial stripping the basement membrane* (triangles) *remained intact. Superficial stroma appears normal. (Owl monkey wearing a 0·4 mm thick HEMA lens for 48 hours, closed eye, × 34 000).*

deprivation, and the consequent changes could involve the water metabolism both of the epithelium and of the deeper corneal layers. On the other hand loss of surface cells, flattening of the layers, and dragging apart of the cell pattern with the development of intercellular spaces may be ascribed to direct mechanical trauma.

According to Polse and Mandell[7] the minimum pressure of oxygen, below which stromal oedema occurs, is in the region 11 to 19 mmHg. These figures are a guide of the limits of normality. For a contact lens on the eye the lens Dk/L for both the open eye state and the closed eye state can be calculated from Fatt and St Helen's figures.[4] Thus the open eye lens needs a Dk/L of 5 to 10×10^{-9} and the closed eye lens a Dk/L of 20 to 40×10^{-9} respectively. Table 2 shows that the thin lenses used satisfy these normality criteria for the open eye state only. The experiments with the open eye and thin lenses show, apart from a mild surface cell disturbance, no cellular abnormalities. This would confirm the criteria of Polse and Mandell.[7] When the Dk/L for the thicker lenses are considered, one must expect according to Fatt and St Helens[4] for the 0·2 mm thick lens a contact lens interface oxygen tension of 8 mmHg and for the 0·4 thick lens a tension of 1 to 2 mmHg for the open eye condition, but for the closed eye state both lenses would produce a zero oxygen tension.

The wearing of medium to thick hydrogel lenses (0·2–0·4 mm) for periods up to 15 hours with open eyes resulted in significant morphological changes in the epithelium. The epithelial thinning observed in these corneas was due to loss of cells and a flattening of the remaining ones. The cytoplasm of the surviving cells was normal except for the surface cells. The absence of epithelial oedema and the lack of abnormalities in organelles such as mitochondria suggest that anoxia has not greatly affected these cells. However, Hamano and Masaki[8] have shown that mitosis decreases in the anoxic cornea, but reduced mitosis can hardly be the explanation to the loss of cells that occurred in the relatively short experimental period. The deformation of the remaining cells and sometimes also their nuclei suggests that the lens weight and lid pressure are factors in contact lens wearers, and in the absence of cytoplasmic abnormalities and oedema it is quite possible that the loss of cells is best explained by such forces. In contrast the rigid non-gas-permeable lens produced oedema and cytoplasmic changes in the epithelium.[3]

Whether the loss of epithelial cells in hard lens wearing corneas is due to trauma or anoxia may be settled only by experiments with hard gas-permeable lenses. Alternatively, it is possible that irritation induced by a rigid lens causes reflex tearing, which owing to the hypotonicity of such tears results in epithelial oedema.[9] Another possible cause of epithelial oedema may be the presence of stromal oedema. Bergmanson and Chu[3] reported significant stromal oedema in rigid lens wearing eyes after 24 hours, while none was seen in the open eye part of the experiments in the present study.

The thick (0·4 mm) HEMA lens under closed eye conditions caused large areas of epithelial stripping. Spaces were found between cells in the areas where epithelial cells were still present. Such spaces are interpreted here as indicative of oedema. The appearance of small separations between the basal cells and the basement membrane suggested that these cells were less firmly attached to the underlying cornea. Significant oedema of the stroma was noted in this cornea, and this may explain the presence of oedema among surviving epithelial cells. The basement membrane remained intact in all regions, including the areas of epithelial stripping. A similar resistance to damage of the basement membrane was also noted in the rigid lens wearing monkey.[3 10] The regrowth of epithelial cells is greatly facilitated by the presence of an intact basement membrane, since migrating cells do not have to secrete a new membrane.

As reported previously, the epithelial nerve fibres were observed in the basal cell layer, where they remained close to the internal aspect of the cell.[11] In contrast to stromal fibres the epithelial axons were without Schwann cells. Unless the epithelium was severely insulted by a soft lens, its nerve fibres remained present in apparently normal numbers. Although large terminals are not a common finding in the epithelium, they were nevertheless observed in the 0·4 mm thick HEMA lens wearing cornea and open eye cornea. Since nerve fibres of an origin other than sensory have not been proved to be present in the primate corneal epithelium, we conclude that the observed axons are somatic sensory. The large number of mitochondria present and the absence of synaptic vesicles in these terminals support this view, though we recognise that an accumulation of mitochondria in a terminal does not allow a positive identification of origin.[12] The favourable response of epithelial nerve fibres to soft lens wear correlates well with clinical experience.[13] Polse[14] showed that the corneal touch threshold is not related to the availability of oxygen. It is therefore likely that the dramatic loss of sensitivity experienced with rigid PMMA lenses is associated with trauma and oedema as well as adaptation to mechanical stimulus.

CONCLUSIONS

1. Thin (0·07 mm) hydrogel (38–43% water) contact lenses worn under open eye conditions in the owl monkey caused no significant epithelial insult.
2. Medium to thick (0·2–0·4 mm) hydrogel contact lenses worn under open eye conditions resulted in a thinning of the epithelium from loss of cells and a flattening of the remaining ones. Since this thinning of the epithelium occurred without oedema, it would be difficult to discover with the slit lamp.
3. The thick (0·4 mm) hydrogel contact lens under closed eye condition caused epithelial oedema and in large areas corneal denudation.
4. In none of the experiments was the basement membrane damaged. The closed eye experiment, which in places stripped the epithelium and thereby exposed the membrane, proved the durability of this structure.
5. Soft contact lens wear had no detectable effect on the epithelial innervation as long as there was not oedema.

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References

1 Francois J. The rabbit corneal epithelium after wearing hard and soft contact lenses. *Contact Intraoc Lens Med J* 1983; **9:** 267–74.

2 Ruben M. *Soft contact lenses*. New York: Wiley, 1978: 294–7.

3 Bergmanson JPG, Chu L W-F. Corneal response to rigid contact lens wear. *Br J Ophthalmol* 1982; **66:** 667–75.

4 Fatt I, St Helen R. Oxygen tension under an oxygen permeable contact lens. *Am J Optom Physiol Opt* 1971; **49:** 545–55.

5 Hogan MJ, Alvarado JA, Wedell JE. *Histology of the human eye*. Philadelphia, London, Toronto: Saunders, 1971: 55–111.

6 Kuwabara T. Current concepts in anatomy and histology of the cornea. *Contact Intraoc Lens Med J* 1978; **4:** 101–32.

7 Polse KA, Mandell R. Etiology of corneal striae at hydrogel lens wear. *Invest Ophthalmol Vis Sci* 1976; **15:** 553–6.

8 Hamano H, Masaki H. Effect of contact lens wear on the mitosis of corneal epithelial cells. *Contact Intraoc Lens Med J* 1983; **9:** 133–6.

9 Schoessler JP, Lowther GE. Slit lamp observations of corneal edema. *Am J Optom Physiol Opt* 1971; **48:** 666–71.

10 Bergmanson JPG, Chu L W-F. Contact lens induced corneal epithelial injury. *Am J Optom Physiol Opt* 1982; **59:** 500–6.

11 Lim CH, Ruskell GL. Corneal nerve access in monkeys. *Graefes Arch Klin Exp Ophthalmol* 1978; **208:** 15–23.

12 Bergmanson JPG. Ophthalmic terminals in the iris and the ciliary body of monkeys. *Graefes Arch Klin Exp Ophthalmol* 1978: **206:** 39–47.

13 Millodot J. Effect of the length of wear of contact lenses on corneal sensitivity. *Acta Ophthalmol (Kbh)* 1976; **54:** 721–30.

14 Polse KA. Etiology of corneal sensitivity changes accompanying contact lens wear. *Invest Ophthalmol Vis Sci* 1978; **17:** 1202–6.

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Measurement of total IgE antibody levels in lacrimal fluid of patients suffering from atopic and non-atopic eye disorders. Evidence for local IgE production in atopic eye disorders?

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SUMMARY Total IgE levels in lacrimal fluid of patients suffering from different eye disorders were quantitatively measured by a modification of the paper radio immuno sorbent test (PRIST). The geometric mean values for patients with atopic conjunctivitis, patients with keratoconjunctivitis vernalis, and patients with asthma without conjunctivitis differed significantly from those for control persons and those for patients without atopic conjunctivitis. Besides lacrimal fluid IgE levels, serum IgE levels as well as lacrimal fluid and serum albumin levels were measured. From these values the local IgE production was calculated. Although there seemed a good correlation between the level of lacrimal fluid IgE and the amount of local IgE production, the results suggest that local IgE production in lacrimal fluid is *not* restricted to patients with atopic *eye* disorders only.

Since the discovery of IgE[1 2] this immunoglobulin has been closely associated with allergic disorders. Radioimmunoassays have been developed to measure total and specific IgE antibody levels, namely, the paper radio immuno sorbent test (PRIST) and the radio allergo sorbent test (RAST). Reports concerning total IgE values in lacrimal fluid have been scarce.[3-6] Since total IgE levels in lacrimal fluid seemed very low, a modification of the PRIST was used to determine quantitatively the IgE content of lacrimal fluid of controls, patients with non-atopic conjunctivitis, different atopic eye disorders, and with asthma without conjunctivitis. Measurement of the serum IgE, the albumin content of serum and lacrimal fluid, enabled calculation of the local IgE production in the same individuals.

Materials and methods

SUBJECTS

All individuals attended the outpatient department of the Clinic of Ophthalmology. The following groups were selected: (1) Normal controls (n=16: age 20–50 years). (2) Non-atopic conjunctivitis (n=20: age 11–71 years), no atopic history, negative skin tests, symptoms of conjunctivitis. (3) Atopic conjunctivitis: seasonal conjunctivitis (n=25: age 8–79 years), seasonal symptoms of conjunctivitis, positive skin tests with or without positive atopic history; chronic conjunctivitis <3 years (n=19: age 11–65 years), chronic symptoms of conjunctivitis for less than three years, positive skin tests with or without positive atopic history; chronic conjunctivitis ≥3 years (n=17: age 15–72 years), chronic symptoms of conjunctivitis for over three years, positive skin tests with or without positive atopic history. (4) Keratoconjunctivitis vernalis non-atopic (n=9: age 8–19 years), no atopic history, negative skin tests. (5) Atopic asthma without conjunctivitis (n=9: age 7–19 years), with atopic asthma without complaints of conjunctivitis.

The diagnosis atopy was based on the results of intracutaneous skin testing. All allergen extracts came from HAL (Haarlems Allergenen Laboratorium Haarlem, The Netherlands). A control prick test with histamine 1:100 000 was included. If two or more intracutaneous skin tests were found positive, the subject was considered to have an atopic constitu-

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tion. On this basis the conjunctivitis group was subdivided into an atopic and a non-atopic group.

LACRIMAL FLUID

Tears were collected by means of a glass capillary (300–600 μl). The lacrimal fluid was stored in polystyrene tubes at −70°C until analysis. In four cases the amount of lacrimal fluid collected was too small to be analysed. These cases were omitted from the study.

NASAL AND CONJUNCTIVAL SMEARS

Smears of nasal secretions and conjunctival scrapings were examined in all subjects and stained with Giemsa. Eosinophilia was graded on a nominal scale, namely, mild, moderate, and severe (1+, 2+, and 3+).

IgE DETERMINATION

The total IgE content of the different *sera* was measured with the commercially available Phadezym-PRIST (Pharmacia, Uppsala, Sweden). The determination and calculation of the serum IgE content (expressed in IU/ml) were performed according to the manufacturer's instructions. The total IgE content in *lacrimal fluid* was measured with a modification of the commercially available PRIST (Pharmacia, Uppsala, Sweden).

The modification of this assay (Johansson SGO, personal communication) deviated on several points from the normal assay procedure: (1) The incubation volume of standard of unknown sample was enlarged to 300 μl. (2) A standard curve was constructed from 0·005 IU/ml to 20 IU/ml (1 IU/ml=2·4 ng/ml). (3) After addition of standard or unknown sample to the anti-IgE disc the incubation tubes were covered with plastic film and were incubated for ±20 hours at room temperature under continuous shaking. Furthermore the procedure was kept similar to the unmodified assay. Since very small quantities of lacrimal fluid were collected (300–600 μl), only single determinations were performed. Although this may have influenced the accuracy of the IgE measurements, the introduction of an IgE reference (0·110 IU/ml) giving reproducible results, convinced us of the reliability of the measured values.

ALBUMIN DETERMINATION

The albumin content was determined by radial immuno diffusion: serum albumin content was determined with NOR-partigen-albumin plates and lacrimal albumin content was determined with LC-partigen-albumin plates (Behringwerke AG, Marburg, Germany). In 12 cases the lacrimal albumin content could not be determined. These cases were excluded from the study.

CALCULATION OF THE LOCAL IgE PRODUCTION

The local IgE production in lacrimal fluid was calculated according to the following formula[7]:

$$\text{Local IgE production} = \text{IgE (lacr)} - \frac{\text{albumin (lacr)}}{\text{albumin (serum)}} \times \text{IgE (serum)}.$$

(Lacr=lacrimal).

Results

TOTAL IgE AND ALBUMIN VALUES IN SERUM AND LACRIMAL FLUID

The total IgE and albumin values in the sera and lacrimal fluid of the different investigated groups are summarised in Table 1. As can be seen from the table, there is a fair interindividual variance in serum and lacrimal IgE values within each group. The geometric mean values of the serum IgE values of the different atopic conjunctivitis groups, the keratoconjunctivitis vernalis group, and the asthma without conjunctivitis group differed significantly from those of the controls and the non-atopic conjunctivitis group. In the case of lacrimal fluid IgE values also the non-atopic conjunctivitis group differed significantly from the normal controls. When the results of the total IgE measurements in serum and lacrimal fluid are compared, it seems as if in lacrimal fluid the difference between the geometric mean values of the controls and the other groups was more striking.

The serum albumin values of the different groups were within the same range. However, the mean lacrimal fluid albumin values of most of the atopic conjunctivitis groups and the keratoconjunctivitis vernalis group were significantly higher than those of the non-conjunctivitis groups (controls, asthma without conjunctivitis).

LOCAL IgE PRODUCTION IN LACRIMAL FLUID

The calculated local IgE production (see 'Materials and methods') in lacrimal fluid of the different investigated groups is shown in Table 2. Within each group the local IgE production also showed a fair interindividual variance. The geometric mean values for the local IgE production in lacrimal fluid of all the atopic groups and the keratoconjunctivitis vernalis group differed significantly from those of the controls and the non-atopic conjunctivitis group. As can be seen from Table 2 the seasonal conjunctivitis group showed the most pronounced local IgE production. Furthermore this table illustrates that the atopic conjunctivitis group and the asthma group without conjunctivitis had a larger percentage of cases with positive local IgE production than the normal control group, the non-atopic conjunctivitis group, or the keratoconjunctivitis vernalis group. Within the atopic conjunctivitis group the percentage of patients

Table 1 *Serum and lacrimal fluid IgE (in IU/ml) and albumin (in mg/ml) in normal controls and patients suffering from conjunctivitis. Geometric mean values +95% confidence intervals are presented*

Clinical groups	*n*	*IgE*		
		Serum		*Lacrimal fluid*
		Geometric mean	*Student's t test*	*Geometric mean*
Controls	16	19·5 (1·4– 273·1)		0·058 (0·012– 0·287)
Non-atopic conjunctivitis	20	24·3 (1·2– 507·8)	NS	0·165 (0·007– 4·137)
Atopic conjunctivitis				
I seasonal	25	262·4 (14·4– 4769·5)	p<0·001	5·259 (0·053– 523·219)
II chronic <3 jr	19	131·6 (0·8–22471·4)	p<0·02	2·581 (0·006–1152·859)
III chronic >3 jr	17	208·5 (7·1– 6124·2)	p<0·001	4·464 (0·066– 304·905)
Keratoconjunctivitis vernalis (non-atopic	9	88·0 (10·2– 765·1)	p<0·01	1·890 (0·242– 14·880)
Asthma without conjunctivitis (atopic)	9	578·3 (105·6– 3165·3)	p<0·001	6·554 (0·819– 52·457)

Statistical analysis was performed according to Student's *t* test.

having a positive local IgE production was greater in the chronic atopic conjunctivitis group than in the seasonal conjunctivitis group.

The correlation between the serum IgE levels and the lacrimal fluid IgE levels on the one hand and the local IgE production on the other hand was calculated. There was a poor correlation between the serum IgE levels and the local IgE production ($r=0\cdot49$; $p<0\cdot001$; Spearman rank correlation). However there was a fairly good correlation between the lacrimal fluid IgE levels and the local IgE production ($r=0\cdot75$; $p<0\cdot001$, Spearman rank correlation). This correlation was more striking when lacrimal fluid IgE levels were over 1 IU/ml.

Discussion

Since the discovery of IgE several methods have been developed to determine total IgE levels quantitatively in various body secretions. Several authors[3–6] have demonstrated the presence of IgE in lacrimal fluid. Brauninger and Centifanto[3] performed semi-quantitative measurements. Their total IgE values ranged from 687·5 to 1083·3 IU/ml. Allansmith *et al.*[4] determined lacrimal IgE by the radio immuno sorbent technique (RIST). The lowest level of IgE in lacrimal fluid they measured at that time was 10 IU/ml in a normal control person. Ballow and Mendelson[5] measured total IgE in lacrimal fluid by the PRIST. The lowest level was measured in the lacrimal fluid of a patient with keratoconjunctivitis vernalis with positive tear RAST but negative skin tests and negative serum RAST and amounted 0·25 IU/ml. Liotet *et al.*[6] have also performed quantitatively total IgE measurements in lacrimal fluid by means of the PRIST. They were able to measure only total IgE levels above 0·5 IU/ml. Our investigation shows that by using a modification of the PRIST much lower IgE levels (lowest level is 0·015 IU/ml) in lacrimal fluid may also be measured with reasonable accuracy. If enough lacrimal fluid can be collected (i.e., >300 μl), the IgE level can always be determined quantitatively with this modification.

As with serum total IgE levels there is a large interindividual variation in the lacrimal fluid IgE levels in the different groups investigated. However,

Table 2 *Local IgE production in lacrimal fluid of normal controls and patients suffering from non-atopic conjunctivitis, different forms of atopic conjunctivitis, keratoconjunctivitis vernalis, and asthma without conjunctivitis. Geometric mean values + 95% confidence interval are presented*

Clinical groups	*n*	*Geometric mean*	*Student's t test*
Controls	16 (7)	0·030 (0·007– 0·134)	
Non-atopic conjunctivitis	20 (9)	0·066 (0·003– 1·377)	NS
Atopic conjunctivitis			
I seasonal	25 (17)	8·653 (0·262–287·149)	p<0·001
II chronic <3 yr	19 (15)	2·096 (0·005–908·686)	p<0·005
III chronic >3 yr	17 (15)	1·954 (0·021–181·999)	p<0·001
Keratoconjunctivitis vernalis (non-atopic)	9 (5)	0·725 (0·095– 5·540)	p<0·001
Asthma without (atopic) conjunctivitis	9 (9)	3·353 (0·185– 60·946)	p<0·001

Statistical analysis was performed according to Student's t test.
The numbers of subjects showing a positive local IgE production are in parentheses.

non-atopic conjunctivitis, different forms of atopic conjunctivitis, keratoconjunctivitis vernalis, and asthma without

	Albumin			
	Serum		*Lacrimal fluid*	
Student's t test	*Geometric mean*	*Student's t test*	*Geometric mean*	*Student's t test*
	41·68 (35·16–49·40)		0·153 (0·019–1·221)	
p<0·025	0·04 (34·34–46·70)	NS	0·232 (0·030–1·822)	NS
p<0·001	41·68 (34·32–50·62)	NS	0·333 (0·033–3·320)	p<0·05
p<0·001	41·68 (38·32–45·33)	NS	0·326 (0·037–2·886)	p<0·05
p<0·001	41·26 (34·12–49·90)	NS	0·419 (0·038–4·618)	p<0·01
p<0·001	42·52 (33·65–53·73)	NS	0·589 (0·063–5·419)	p<0·01
p<0·001	42·10 (35·30–50·20)	NS	0·170 (0·028–1·030)	NS

comparison of the calculated geometric mean values of the lacrimal fluid IgE levels and the serum IgE levels shows that the difference between the different patients groups and the normal control group is greater in lacrimal fluid than in serum. This could be considered an indication for local IgE production, and generally the higher the lacrimal fluid IgE content the stronger the local IgE production. If the lacrimal fluid IgE content is below 1 IU/ml, it becomes difficult to predict the local IgE production. Some individuals with lacrimal fluid IgE levels below 1 IU/ml showed local IgE production where others did not. On the contrary most of the individuals with lacrimal IgE values >1 IU/ml showed local IgE production (±84% of the investigated individuals). Our study suggests that the stronger the local IgE production the more severe the atopic manifestations. On the other hand a moderate local IgE production may be accompanied by severe conjunctivitis. This relation is independent of the kind of conjunctivitis (seasonal or chronic). Therefore it would be interesting to see if there is a seasonal variation in local IgE production as there is with the patients complaints and if both IgE production and complaints decrease during certain form of therapy. This problem is currently under investigation.

Although the above mentioned data seem convincing, one has to realise that the local IgE production is calculated and not measured. Diffusion from the circulation may influence the lacrimal fluid IgE content. In the formula used to calculate the local IgE production albumin is used as a kind of internal standard. Increased albumin levels in lacrimal fluid as seen in atopic conjunctivitis as well as keratoconjunctivitis vernalis may therefore be indicative of the local production of vasodilatory substances or local inflammatory processes. Both may facilitate diffusion of serum IgE and cause increased lacrimal fluid IgE levels. The strong influx of eosinophils in both disease states may be partly responsible for that, since it has recently been established that eosinophils are capable of producing almost exclusively the strong vasoactive leukotriene C4.[8] This finding may be important, since in those cases of atopic asthma without conjunctivitis the albumin content in lacrimal fluid is completely normal and eosinophils are rare. Therefore the eosinophil may be involved in some way in the pathogenesis of atopic conjunctivitis and keratoconjunctivitis vernalis. Nevertheless, in cases of atopic asthma without conjunctivitis a greatly increased local production of IgE has been found (see Table 1). A possible explanation for this finding may be that in atopic individuals in general IgE-producing lymphocytes may be present round most mucosal barriers, and local IgE production is a general feature. Therefore local IgE production in lacrimal fluid is not specific for atopic eye disorders only. This conclusion is in contrast with that of Liotet *et al.*[6] However, they omitted to incorporate a control group of atopic persons without conjunctivitis.

Another explanation may be that measurement of local IgE production is too imprecise to discriminate between different atopic disorders and that specific IgE production may lead to a better discrimination. This will be investigated in the near future.

References

1 Ishizaka K, Ishizaka T, Hornbrook MM. Physicochemical properties of reagine antibody. IV. Presence of a unique immunoglobulin as antibody. *J Immunol* 1966; **97:** 75–85.
2 Johansson SGO, Bennich H. Immunological studies of an atypical (myeloma) immunoglobulin. *Immunology* 1967; **13:** 381–94.
3 Brauninger GE, Centifanto YM. Immunoglobulin E in human tears. *Am J Ophthalmol* 1971; **72:** 558–61.
4 Allansmith MR, Hahn GS, Simon MA. Tissue, tear and serum IgE concentrations in vernal conjunctivitis. *Am J Ophthalmol* 1976; **81:** 506–11.

5 Ballow M, Mendelson L. Specific immunoglobulin E antibodies in tear secretions of patients with vernal conjunctivitis. *J Allergy Clin Immunol* 1980; **66:** 112–8.

6 Liotet S, Warnet VN, Arrata M. Lacrimal immunoglobulin E and allergic conjunctivitis. *Ophthalmologica* 1983; **186:** 31–4.

7 Deuschl H, Johansson SGO. Immunoglobulins in tracheobronchial secretion with special reference to IgE. *Clin Exp Immunol* 1974; **16:** 401–12.

8 Verhagen J, Bruynzeel PLB, Koedam JA, *et al.* Specific leukotriene formation by purified human eosinophils and neutrophils. *FEBS Lett* 1984; **168:** 23–8.

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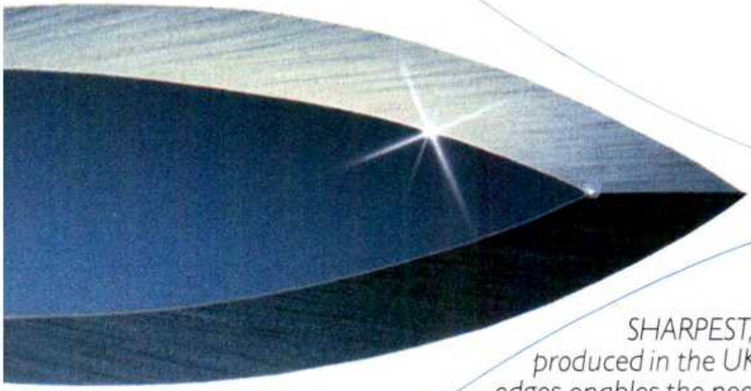

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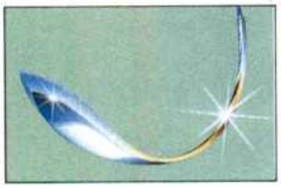

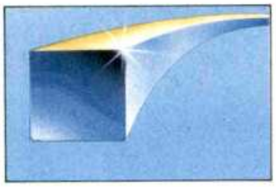

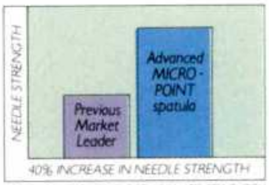

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Prevalence of chlamydial eye infection in patients attending an eye clinic, a VD clinic, and in healthy persons

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SUMMARY Chlamydial eye infection was detected in 28 of 983 ophthalmological patients with conjunctivitis or keratoconjunctivitis, with a peak frequency of over 9% in patients aged 16–20 years and with decreasing frequency thereafter. In patients aged 1 to 15 years chlamydial conjunctivitis was not observed. Chlamydial eye infection could not be detected in patients at a venereal diseases clinic, though chlamydial genital infection was rather frequent in these patients. Nor was *Chlamydia trachomatis* found in the eyes of healthy young adults. In patients with proved chlamydial conjunctivitis unilateral symptoms were the rule. Pseudoptosis was the most conspicuous presentation in two cases. A prolonged course can be expected in chlamydial eye infection if the condition is unrecognised and effective treatment delayed. The venereal background of the condition must also influence the management.

Infections by *Chlamydia trachomatis* are now considered to be one of the major causes of sexually transmitted diseases in the industrialised countries. Besides genital infections, which constitute a considerable public health problem, *C. trachomatis* may cause eye infections. Chlamydial eye infections have been observed in sexually active young adults and in neonates, where the infection has been transmitted to the infant from the mother. The clinical features include conjunctivitis with papillary and follicular reaction (inclusion conjunctivitis); corneal lesions (keratitis punctata); and invasion of the cornea by blood vessels (pannus), a condition indistinguishable from trachoma.[1 2] Tarsal scarring may eventually develop in some cases. Follicles are seldom found in infants, as tarsal lymphoid tissue is scarce. Chlamydial disease of sexual origin with genital and eye manifestations has been designated paratrachoma. Classical endemic trachoma can usually be separated from paratrachoma on epidemiological, serological, and often clinical grounds. Endemic trachoma is usually seen as an intrafamilial infection in underprivileged areas of the world, with the highest incidence in early childhood.[3] Recurrences and reinfections, usually within the family group, are part of the disease. Chlamydial strains isolated from patients with endemic trachoma usually belong to the serovarieties A, B, Ba, and C. Strains of genital origin can generally be assigned to the serovarieties D-K, with few exceptions.[4]

The causative role of *C. trachomatis* in inclusion conjunctivitis has been established by experimental inoculation of the eyes of volunteers.[5] The venereal nature of inclusion conjunctivitis has also been repeatedly confirmed.[6-8] In some situations, however, eye-to-eye transmission seems likely or at least has been suggested—for example, siblings and relatives to infants with inclusion blenorrhea, and medical personnel.[9-11] Chlamydial eye infection has also been associated with swimming pool bathing.[12]

In this investigation clinical and epidemiological aspects of chlamydial eye infections were studied in patients attending an eye clinic because of symptoms of conjunctivitis. The prevalence of *C. trachomatis* eye infection in patients at a venereal diseases clinic and in a group of healthy young adults was also assessed.

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Materials and methods

Ophthalmological patients. Patients seen at the Department of Ophthalmology at Malmö General Hospital with conjunctivitis and keratitis were included in the study. For practical reasons all patients with conjunctivitis could not be examined for chlamydial infection. Although there was no conscious selection of patients, a bias was probably introduced in the material because patients with longstanding symptoms, and therefore with repeated visits to the department, would be more likely to have a chlamydial culture than the average patient. The department serves the whole city of Malmö, with a population of a quarter of a million people. For patients with acute eye symptoms few other medical facilities are available, and therefore patients seen at the hospital are likely to constitute a representative cross-section of the community.

Eye swabs for chlamydial isolation were obtained from 983 patients during a period of four years, and all these patients were examined with a corneal microscope.

STD patients. All patients attending the clinic for sexually transmitted diseases (STD patients) with suspected venereal disease were examined for chlamydial eye infection in addition to genital culture. During four months 855 patients were studied. A cotton-wool swab was obtained from each eye.

Healthy young adults. Healthy persons aged 16 to 25 years seeking public employment were examined by eye swabs for chlamydial eye infection at a routine medical check-up. Altogether 127 persons were examined.

Chlamydial isolation. Cotton-wool tipped swabs were used to get specimens for isolation of *C. trachomatis*. Swabs were placed in a transport medium of sucrose-containing phosphate buffer (2 SP), which was used to inoculate cell cultures of irradiated McCoy cells on round cover slips. Each specimen was inoculated in duplicate. After incubation at 37°C for 72 hours typical chlamydial inclusions were detected after iodine staining.

Results

Ophthalmological patients. Of the 983 patients examined for *C. trachomatis* in the eyes 61% were females; they included patients of all ages from 1 year upwards. Chlamydial eye infection was demonstrated in 28 patients, of whom 64% were females. As seen in Table 1 chlamydial eye infection was not detected in patients under 16 years of age or older than 40 years. The highest frequency of chlamydial eye infection of over 9% was found at ages 16–20 years. The frequency decreased gradually with increasing age. The mean age of the patients with chlamydial eye infection was 23 years. Microbiological examination in 26 of the chlamydia positive cases did not show any additional bacterial pathogen in the eyes. A genital examination was performed on nine of the 18 females with chlamydial conjunctivitis, and genital chlamydial infection was detected in five of these patients. A single male of the 10 with positive eye culture was also examined by urethral culture which yielded *C. trachomatis*.

Clinical symptoms from the eyes in chlamydial infection were unilateral in 20 cases, and in the remaining eight cases with bilateral infection symptoms were generally more pronounced in one eye. Follicular conjunctivitis was regularly seen in cases of some duration. Corneal lesions observed included keratitis punctata, and marginal as well as central infiltrates clinically similar to those associated with adenovirus infection. Vascular infiltration of the cornea was not observed. Two cases had unilateral pseudoptosis as the most conspicuous symptom.

Table 1 *Chlamydial eye and genital infection according to age in different patient categories*

Age groups (years)	*Ophthalmologic patients: chlamydial conjunctivitis, number examined*	*VD patients: genital chlamydial infection, number examined*		*Healthy adults: chlamydial eye infection, number examined*
		females	*males*	
1–5	0/90	—	—	—
6–10	0/40	—	—	—
11–15	0/47	3/7 (43%)	0/2	—
16–20	13/147 (9·3%)	23/84 (27%)	18/78 (23%)	0/77
21–25	8/153 (5·2%)	19/76 (25%)	34/155 (22%)	0/50
26–30	5/123 (4·1%)	6/53 (11%)	20/131 (15%)	—
31–35	1/84 (1·2%)	1/21 (5%)	19/97 (20%)	—
36–40	1/67 (1·5%)	2/19 (11%)	10/46 (22%)	—
41–	0/240	1/21 (5%)	3/65 (5%)	—
Total	28/983 (2·8%)	55/281 (19·6%)	104/574 (18·1%)	0/127

Eye symptoms had persisted for days to several months when chlamydial eye infection was confirmed. The mean duration of symptoms was about five weeks when proper diagnosis was secured.

One of the women developed chlamydial eye infection a few days after the same condition had been diagnosed in her baby. A male patient revealed that he and his fiancé had the same symptoms from the eyes, but a chlamydial isolate could be secured only from the man, as his girl friend lived in another town.

Patients with chlamydial eye infection were treated with oral doxycyclin 100 mg a day for nine days. One nursing mother was given erythromycin 1 g a day instead. Topical chloramphenicol or chlortetracycline hydrochloride eye ointment was also used regularly to prevent possible superinfection. With this regimen the infection subsided and signs of activity had disappeared within 2–3 weeks. Follicles and corneal non-active opacities could be detected for weeks to some months after systemic treatment was finished. Twenty-three patients with chlamydial eye infection could be followed up until the condition healed, which took on average about two months after diagnosis. Nine patients had control cultures taken on average 13 days (range 2–30 days) after treatment, which were all negative.

STD patients. Of the 855 patients examined by genital and eye swabs for chlamydial infection 67% were males, of whom 104 had genital chlamydial infection. *C. trachomatis* was detected in genital swabs among 55 of 281 females. In no case was chlamydial eye infection demonstrated. The mean age of males with genital chlamydial infection was 27 years and 24 years for females with *C. trachomatis* infection.

Healthy adults. Swabs from the eyes for chlamydial isolation were obtained from 127 healthy employees. *C. trachomatis* was not isolated in any case. Of this group 80% were females. The mean age in the whole group was 20 years.

Discussion

Chlamydial eye infection was found with the highest frequency among young adults at 20 to 25 years of age. This is the same age at which genital chlamydial infection was most common among the VD patients. Chlamydial salpingitis and genital chlamydial infections in puerperal women in our series are also most prevalent at 15 to 25 years of age.[13 14] Although *C. trachomatis* was not uncommon at these ages among the ophthalmological patients, it was not isolated from the eyes of any of the 855 VD patients, of whom 159 had genital chlamydial infection. In patients with chlamydial eye infection more than half of those examined had concomitant genital chlamydial infection. In the VD patients we detected genital chlamydial infection in 18% of male patients and 20% of females. In earlier studies we found genital infection by *C. trachomatis* in 25% of the female patients at the VD clinic, in 5% of women at a health care centre,[15] and in 2·4% of puerperal women.[14]

These figures demonstrate a much higher frequency of genital chlamydial infection among the ophthalmological patients with chlamydial eye infection than for the average population and underline the venereal nature of chlamydial eye disease. Asymptomatic carriers of *C. trachomatis* in the eyes seem to be uncommon in VD patients and healthy adults and would suggest that, when present, chlamydial eye infection is generally accompanied by disquieting symptoms from the eyes. Therefore these patients are often seen by the ophthalmologist and not by the venereologist or the gynaecologist, though genital symptoms may also be present. It is also noteworthy that other pathogenic bacteria were not disclosed in 26 of the 28 cases with chlamydial conjunctivitis. In two cases bacterial cultures were not performed.

One case with chlamydial conjunctivitis was encountered in which non-venereal transmission may have occurred. Chlamydial eye infection developed in a nursing mother a few days after chlamydial conjunctivitis had been confirmed in her 2-weeks-old baby. Autoinfection in the mother is possible, but eye-to-eye transmission between infant and mother also seems likely.

It seems that chlamydial eye infection is manifested in a minority of patients with chlamydial infection. In our laboratory, which has about 700 to 800 chlamydial isolates a year, 7 to 10 come from adults with chlamydial conjunctivitis. A rough estimate would then be that between 1 and 2% of chlamydial infections are accompanied by eye symptoms.

Symptoms were unilateral in the majority of cases, indicating that autoinfection from one eye to the other is limited. In two cases unilateral pseudoptosis without other signs of cranial nerve paralysis was the most conspicuous symptom. The pseudoptosis was due to subtarsal swelling and follicles and disappeared completely after treatment.

It was also evident that symptoms could persist for weeks and months if a correct diagnosis and treatment were delayed. In our material the proportion of patients with longstanding eye symptoms may be exaggerated, as these patients were more likely to be examined for chlamydial infection. On the other hand they show that chlamydial conjunctivitis may have a lingering course, involving repeated consultations, if the true nature of the condition is not suspected and proper therapy therefore not given. After effective treatment corneal inactive opacities persisted, in some cases for several weeks before they resolved in all the 23 patients whom it was possible to follow up.

Treatment must aim at eradication of chlamydial infection in both the eyes and the genital tract. This goal can be achieved by systemic therapy with either tetracyclines or erythromycin, probably with similar efficacy. In pregnant women or nursing mothers tetracyclines must be avoided. Erythromycin is therefore the obvious choice in these special situations. Consorts to patients with chlamydial conjunctivitis are very likely to have genital chlamydial infection. Chlamydial salpingitis and perhaps infertility in the female is probably the most ominous aspect of chlamydial infection, which should be remembered when dealing with infections by *C. trachomatis*.

References

1 Jones BR. Ocular syndromes of TRIC virus infection and their genital significance. *Br J Vener Dis* 1964; **40:** 3–18.

2 Viswalingam ND, Wishart MS, Woodland RM. Adult chlamydial ophthalmia (paratrachoma). *Br Med Bull* 1983; **39:** 123–7.

3 Darougar S, Jones BR. Trachoma. *Br Med Bull* 1983; **39:** 117–22.

4 Grayston JT, Wang SP. New knowledge of chlamydiae and the diseases they cause. *J Infect Dis* 1975; **132:** 87–105.

5 Jones BR, Collier LM. Inoculation of man with inclusion blenhorrhae virus. *Ann NY Acad Sci* 1962; **98:** 212–26.

6 Jones B, Al-Hyssain K, Dunlop E. Infection of the eye and genital tract by TRIC agent: III Ocular syndromes associated with infection of the genital tract by TRIC agent. *Rev Int Trach Pathol Ocul Trop Subtrop* 1965; **42:** 27–43.

7 Dawson CR, Schachter J. TRIC agent infections of the eye and genital tract. *Am J Ophthalmol* 1967; **63** (suppl): 1288–98.

8 Schachter J, Rose L, Meyer KF. The venereal nature of inclusion conjunctivitis. *Am J Epidemiol* 1967; **85:** 445–52.

9 Rees E, Tait IA, Hobson D, Byng RE, Johnson FWA. Neonatal conjunctivitis caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. *Br J Vener Dis* 1977; **53:** 173–9.

10 Julianelle LA, Harrison RW, Lange A. Studies on inclusion blennorrhea. *Am J Ophthalmol* 1938; **21:** 1230–41.

11 Thygeson P, Stone W. Epidemiology of inclusion conjunctivitis. *Arch Ophthalmol* 1942; **27:** 91–122.

12 Huntemüller, Paderstein. Chlamydozoen-Befunde bei Schwimmbad-conjunctivitis. *Dtsch Med Wochenschr* 1913; **36:** 63–66.

13 Osser S, Persson K. Epidemiologic and serodiagnostic aspects of chlamydial salpingitis. *Obstet Gynecol* 1982: **59:** 206–9.

14 Persson K, Rönnerstam R, Svanberg L, Holmberg L. Maternal and infantile infection with chlamydia in a Swedish population. *Acta Paediatr Scand* 1981; **70:** 101–5.

15 Persson K, Persson K, Hansson H, *et al.* Prevalence of nine different micro-organisms in the female genital tract. A comparison between women from a venereal disease clinic and from a health control department. *Br J Vener Dis* 1979; **55:** 429–33.

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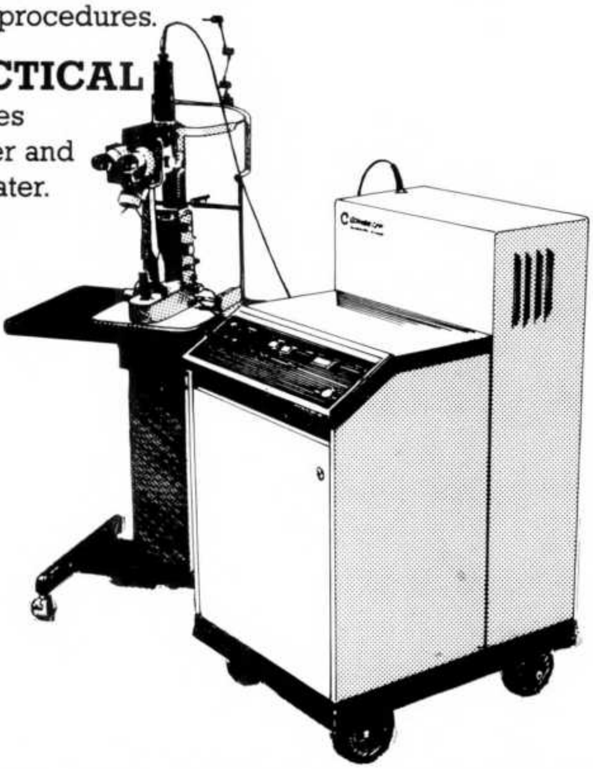

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Common causes of blindness in Zaïre

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SUMMARY An analysis of 50 000 patients' medical records was made to determine the commonest causes of blindness in Zaïre. It was found that the commonest causes of blindness in order of frequency were glaucoma (31%), cataract (18·4%), optic atrophy (16·3%), onchocerciasis (4·9%), and corneal leucoma (4·9%).

The definition of legal blindness varies from one country to another. To give one example of the differences, the legally blind in the USA are those whose corrected visual acuity for distance is equal or inferior to 20/200 (6/60) or with a visual field not greater than 20° in the better eye.[1 2] But in many European and African countries persons with legal blindness are those whose corrected visual acuity is equal or inferior to 1/20 (3/60) or whose visual field is not greater than 10° in the better eye.

Studies of the predominant causes of blindness have been performed for a number of countries with different results from one country to another and in the same country from one region to another (regions of endemic onchocerciasis or trachoma, rural or urban).

The world can be schematically divided into developed and developing countries. In the first group the main causes of blindness are ocular degenerative diseases (macular degeneration, degenerative myopia, glaucoma) and diabetic retinopathy.[1 3–5] In the second group the predominant causes of blindness are ocular infections (onchocerciasis, trachoma, keratoconjunctivitis, and corneal ulcers), malnutrition (xerophtalmia, keratomalacia, optic neuritis), glaucoma, and cataract.[2 3 6–11]

In Zaïre our study of the main causes of blindness had two purposes: (1) to determine the ocular diseases which cause blindness; (2) to provide prophylactic and curative treatment of them.

Materials and methods

From 1962 to 1979 50 000 patients have been treated at the Eye Department of University Hospital of Kinshasa. The patient's identity (age, sex, ethnic group, and profession), his visual acuity, visual field, and results of biomicroscopic, tonometric, and funduscopic examination were noted. The patients with visual acuity equal or inferior to 1/20 (finger counting at 2·5 m) and/or a visual field of less than 10° (Goldmann perimeter) are considered as legal blind.

The diagnosis was made for each eye separately, but in the case of two or more diagnoses—for example, retinal detachment and cataract—retinal detachment was noted the main cause of blindness because it is the most important affection.

We have excluded from this study cases of cataract successfully operated on (with visual acuity superior to 1/20). We consider only cataract which cannot be treated surgically for various psychological reasons (ignorance, patient's refusal).

Results

Of 50 000 patients treated, 944 or 1·9%, were registered as legal blind. Male blind patients were twice as common as female. The age distribution of the legal blind is shown in Table 1. 24% of blind persons less than 20 years old were in the preschool or school period. The age groups 20–44 years old (27·6%) and 45–64 years (32·9%) contained 60% of the legal blind. These persons were at an active stage of life and had various professional and family responsibilities.

The incidence of the principal causes of blindness is shown in Table 1, while the distribution of the causes by sex is shown in Table 2. Glaucoma (31%) was by far the commonest cause of blindness in our sample. Cataract (18·4%) and optic atrophy of various causes came in the second and the third position respectively. Affections of the optic nerve, including glaucoma and atrophy, made 448 patients blind (880 eyes) or about 50%. Onchocerciasis was in the fourth position, with 47 legally blind (4·9%) or 94 eyes. This figure should be regarded as minimal.

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Table 1 *Leading causes of legal blindness for age groups expressed as percentage, Zaïre*

Causes	*Percentage of patients by age groups*					
	0–4	*5–19*	*20–44*	*45–64*	*65–74*	*75 years*
1 Glaucoma	2·1	1·8	7·3	14	4·5	1·5
2 Cataract	3·0	1·6	1·9	6·8	4·6	0·5
3 Optic atrophy	2·5	1·9	6·5	4·4	0·5	0·5
4 Onchocerciasis	—	—	1·4	1·9	1·6	—
5 Corneal leucoma	0·7	0·5	2·8	0·8	—	—
6 Phthsis	0·5	0·5	2·4	0·8	0·6	—
7 Hereditary retinal dystrophies	0·5	0·7	2·0	0·9	0·4	—
8 Retinal detachment	—	0·7	1·6	1·8	0·1	—
9 Congenital anomalies	2·7	1·2	—	—	—	—
All others	1·5	1·6	2·6	1·5	0·4	0·3
Total	13·5	10·5	27·6	32·9	12·7	2·8

Table 2 *Common causes of blindness in males and females, Zaïre*

Causes	*No patients* (%)	*No eyes* (%)	*Male*	*Female*	*Sex ratio*
1 Glaucoma	294 (31·0)	587 (31·8)	192	102	2/1
2 Cataract	174 (18·4)	359 (19·4)	103	71	2/1·5
3 Optic atrophy	154 (16·3)	293 (15·9)	96	58	2/1·6
4 Onchocerciasis	47 (4·9)	94 (5·0)	39	8	5/1
5 Corneal leucoma	47 (4·9)	88 (4·7)	29	18	2/1·6
6 Phthisis	47 (4·9)	88 (4·7)	27	20	2/1·3
7 Hereditary retinal dystrophies	43 (4·5)	86 (4·6)	32	11	3/1
8 Retinal detachment	40 (4·2)	64 (3·5)	32	8	4/1
9 Congenital anomalies	37 (3·9)	74 (4·0)	23	14	2/1·6
10 Chorioretinitis	15 (1·5)	29 (1·6)	8	7	1/1
11 Staphyloma + tumours	13 (1·4)	22 (1·2)	10	3	3/1
12 Degenerative myopia	11 (1·2)	22 (1·2)	6	5	1/1
13 Cortical blindness	9 (0·9)	18 (0·9)	2	7	1/3·5
14 Diabetic retinopathy	7 (0·6)	14 (0·7)	7	0	7/0
15 Vascular occulusions	6 (0·6)	9 (0·5)	3	3	1/1
Total	944 (100)	1847 (100)	609	335	2/1

Discussion

The population of Zaïre is sufficiently well represented by the patients treated at the Eye Department of the University Hospital of Kinshasa. In fact the most serious cases of blindness and visual handicap are usually referred to University Hospital for a second opinion and treatment. Nevertheless, our statistics are minimal, because some blind people cannot consult a physician either through ignorance or for financial or psychological reasons. In addition the University Hospital is situated far from some of the onchocerciasis endemic areas, such as Kasaï-Sankuru (about 800 km); this explains the moderate number of patients blind from onchocerciasis in our sample. The male-to-female ratio of 2:1 among the legal blind is to be expected because of the predominance of male persons attending at the Eye department.

The absence of a policy of registration of blind people by the National Social Security, as in other countries, makes difficult any evaluation of the incidence of blindness for the entire population of Kinshasa.[3 11 12]

In the present study the age at onset of visual defect is difficult to determine because ophthalmic examination usually takes place some time after the onset of blindness. The median time between the onset of the visual defect and diagnosis is two years. The fact that many patients are young is disturbing: 24% of them are in the age group 0–19 years, corresponding to the preschool and school periods. The incidence of blindness increases with advancing age: respectively 52% up to 45 years and 85% up to 65 years.

CAUSES

Glaucoma, accounting for about 31%, is the commonest cause of blindness in our sample. Persons with glaucoma are generally examined very late, and are difficult to treat by either the rigorous application of miotics or by surgical operation. Pilocarpine administered in high concentration (4%, 6%) alone or together with timolol usually gives fairly good tonometric results.[13] But pilocarpine in high concentration is rare on the market and timolol very expensive. Filtering operations for glaucoma (Elliot trepanation, trabeculectomy) can improve or stabilise the glaucoma, but in some cases no improvement is noted.

Cataract, accounting for about 18%, is the second commonest cause of blindness. The contrast between our statistics and those of other studies can be explained as follows: only cataract not treatable surgically is considered here, and cataract treated with visual improvement is excluded from this study. However, the data from the present study show some points which are worthy of comment. Cataract is a specially important cause of blindness, for it affects young people, with high incidence of unilateral cataract. In India and several developing countries cataract is the principal cause of blindness.[2 3 7 8 11 14 15 16]

Optic atrophy ranks as the third cause of blindness. Different causes of it can be suggested: congenital, hereditary, toxic (from trypanosomiasis treatment with tryparsamide injections), infection (meningitis, syphilis), and after head or orbital injuries.

Onchocerciasis appeared as the fourth cause of blindness, but in some endemic areas, and villages, it becomes the commonest cause. In some villages of Kasaï such as Kasongo-Batetela, Lusambo, many persons are affected; they became blind from sclerosing keratitis, secondary glaucoma, Ridley chorioretinitis, optic atrophy, or bulbus atrophy.[17 18]

Trachoma is a chronic keratoconjunctivitis unknown in Zaïre and is absent from our list of blinding ocular diseases. It is a more important cause of blindness in the Eastern Mediterranean, in east, the south, and south-east Asia, in Australia, and in other African countries.[3 11 16]

Xerophthalmia, in its typical form is rarely a cause of blindness in Zaïre. Keratomalacia is commonly observed in children affected by measles complicated by gastroenteritis, bronchopneumonia, malnutrition, and dehydration. It may be a herpetic infection with bacterial superinfection (pseudomonas). It is known that the prevalence of xerophthalmia is high in the rice culture regions of Asia and in other parts of Africa, America, and Asia.[3 11]

The common blinding conditions in developed countries, such as senile macular degeneration, hereditary chorioretinal dystrophies, and diabetic retinopathy are poorly represented in our statistics.[1 2 4 12 19]

References

1 Ghafour IM, Alland D, Foulds WS. Common causes of blindness and visual handicap in the west of Scotland. *Br J Ophthalmol* 1983; **67:** 209–13.

2 Roy FH. World blindness: definition, incidence and major treatable causes. *Ann Ophthalmol* 1974; **6:** 1049–50,

3 World Health Organisation. Prévention de la cécité. *Chronique OMS* 1976; **30:** 437–44.

4 Konstantinov N, Pencheva D. Causes of blindness among children in Bulgaria. *Ophthalmologica* 1977; **175:** 215–21.

5 Robinson GS, Watt JA, Scott E. A study of congenital blindness in British Columbia. Epidemiological findings. *Can J Ophthalmol* 1969; **4:** 152–62.

6 Diallo JS. Causes of blindness in Tropical Africa. *Med Afr Noire* 1977; **24:** 563–6.

7 Massin M, Arrata M. Cécité en 1978. *Concours Med Fr* 1978; **100** (suppl).

8 Olurin O. Etiology of blindness of Nigerian children. *Am J Ophthalmol* 1970; **70:** 533–40.

9 Said ME, Goldstein H, Korra A, El-Kashlan K. Prevalence and causes of blindness in a developing country. A preliminary report. *Sight Sav Rev* 1969; **39:** 158–61.

10 Said ME, Goldstein H, Korra A, El-Kashlan K. Blindness prevalence rates in Egypt. *HSMHA Rep* 1972; **87:** 177–84.

11 Verin PH. Les causes de cécité en Afrique. *Med Afr Noire* 1979; **26:** 23–6.

12 Canadian National Institute of the blind. *Statistical studies on the blind population of Canada registered with CNIB, 1979.* Toronto: CNIB, 1981.

13 Maertens K, Kabuni M. L'effet de la pilocarpine à pourcentage élevé sur l'iris pigmenté. *Bull Soc Belge Ophtalmol* 1982; **201:** 99–104.

14 Chartterjee A, Roy CM, Sydney T. Prevalence and aetiology of cataract in Punjab. *Br J Ophthalmol* 1982; **66:** 35–42.

15 Chartterjee S. Blindness in Ghana and its rehabilitation. *Ghana Med J* 1970; **9:** 314–5.

16 Toufic N. La cécité et ses problèmes en Afrique de l'Ouest d'expression française. *Ann Oculist (Paris)* 1969; **62:** 724–8.

17 Maertens K. Les complications oculaires de l'onchocercose. *Ann Soc Belge Med Trop* 1981; **61:** 199–224.

18 Maertens K. Aspects ophtalmologiques de l'onchocercose au Zaïre. *Ophtalmologie tropicale.* Paris: Lab Merk Sharp and Dohme, 1982.

19 Abramson JM, Kark SL, Michaelson IC, Epstein LM. Prevalence and causes of blindness in Jerusalem. *Isr J Med Sci* 1971; **7:** 268–79.

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Massive juvenile ossifying fibroma of maxillary sinus with orbital involvement

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SUMMARY A 14-year-old black girl had painless, progressive proptosis and upward displacement of the left eye for approximately six months. Computed tomography showed a massive tumour involving the maxillary sinus with extension into the sphenoid sinus, ethmoid sinus, and orbit. The mass was excised surgically and proved histopathologically to be a juvenile ossifying fibroma. The clinical and histopathological features of this uncommon orbital tumour are discussed and its place in the spectrum of fibro-osseous tumours of the orbital region is considered.

Ossifying fibroma is a rather uncommon fibro-osseous tumour which can involve the bones of the orbit and paranasal sinuses and produce proptosis. This tumour has generally been difficult to differentiate clinically and histopathologically from fibrous dysplasia and other fibro-osseous tumours of the orbital region.[1 2] Recent publications, however, have pointed out that it does have certain clinical and histopathological features which serve to differentiate it from other related lesions.[3 4] Some authors have reported that computed tomography can be particularly helpful in diagnosing ossifying fibroma.[4] Most ossifying fibromas in the orbital area have arisen from the orbital plate of the frontal bone or from the ethmoid sinus region, and ossifying fibromas of the maxillary sinus with secondary orbital involvement appear to be quite rare.[5] We report here the case of 14-year-old girl who developed proptosis and upward displacement of the left eye secondary to a massive juvenile ossifying fibroma which arose from the maxillary sinus and secondarily invaded the orbit.

Case report

A 14-year-old black girl with no prior ocular or systemic problems developed slowly progressive proptosis and upward displacement of the left eye over a six-month period. She was referred to the Oncology Service of Wills Eye Hospital for examination and treatment.

Ocular examination disclosed a visual acuity of 6/5 (20/15) in the right eye and 6/7·5 (20/15) in the left eye. The intraocular pressure was 11 Hgmm in both eyes by applanation tonometry. There was obvious proptosis, with upward displacement of the left eye (Fig. 1). There was a slight left exotropia on upgaze and slight limitation of supraduction with the left eye. Hertel exophthalmometry revealed 8 mm of left proptosis, with readings of 18 and 26 for the right and left eyes respectively. No orbital masses could be palpated. Fundus examination revealed no indentation of the globe by an orbital mass and no choroidal folds. Ultrasonography disclosed a large posterior orbital mass with high internal reflectivity.

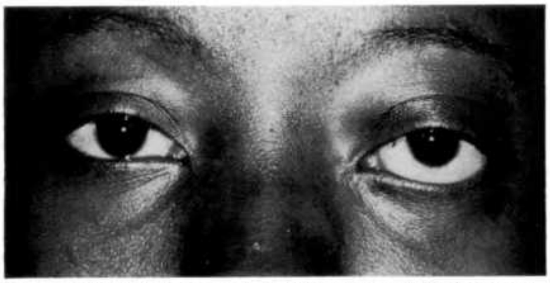

Fig. 1 *Clinical photograph showing upward displacement of the left eye with proptosis.*

Correspondence to Dr J A Shields, Oncology Service, Wills Eye Hospital, Ninth and Walnut Streets, Philadelphia, PA 19107, USA.

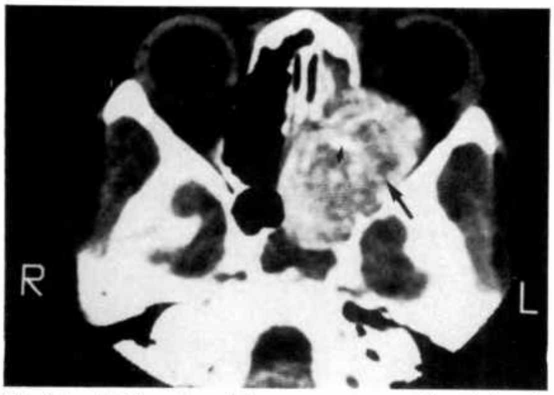

Fig. 2A *Axial section without contrast material at the level of the inferior orbits shows a large, well circumscribed hyperdense mass (large arrow) involving the left ethmoid, upper maxillary, and sphenoid sinuses, with extension well into the left orbit. There are numerous foci of calcification or ossification within the lesion, the most prominent of which is indicated (small arrow). Destruction of the bony margins of the involved sinuses is noted.*

Computed tomography (CT) without contrast material in axial and coronal planes showed a large, well circumscribed mass filling the left maxillary sinus and extending into the left orbit, ethmoid, and sphenoid sinuses, the nasal cavity, and intracranially to the infrafrontal epidural space (Figs. 2A, B, C). The lesion was nonhomogeneous owing to foci of ossification and was predominantly dense relative to brain. Frank bone destruction was noted in several sites, while in other areas bone was displaced around the edge of the lesion. Exophthalmos was noted on the left side.

On the basis of the clinical and CT findings our clinical diagnosis was a fibro-osseous lesion, most likely ossifying fibroma. Under general anaesthesia a Lynch incision was made and extended inferiorly to expose the medial aspect of the maxillary wall. The periosteum was elevated and the thinned anterior maxillary wall was exposed. The large size and unyielding nature of the mass made removal in one piece impossible. Therefore the gritty tumour was removed piecemeal. After complete removal of the mass, which extended into the ethmoid and sphenoid sinuses, the cavity was irrigated and packed with antibiotic-coated new gauze. Blood loss was less than 150 ml and there were no surgical complications. The patient was doing well, with good vision and no systemic or ocular problems approximately three months after the surgery.

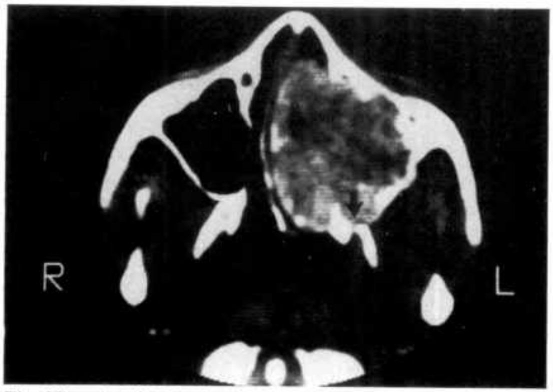

Fig. 2B *Axial CT inferior to that shown in Fig. 2A. The mass fills the left maxillary sinus and most of the left nasal cavity. Destruction of the medial wall of the maxillary sinus and of the left pterygoid bone (arrow) are seen.*

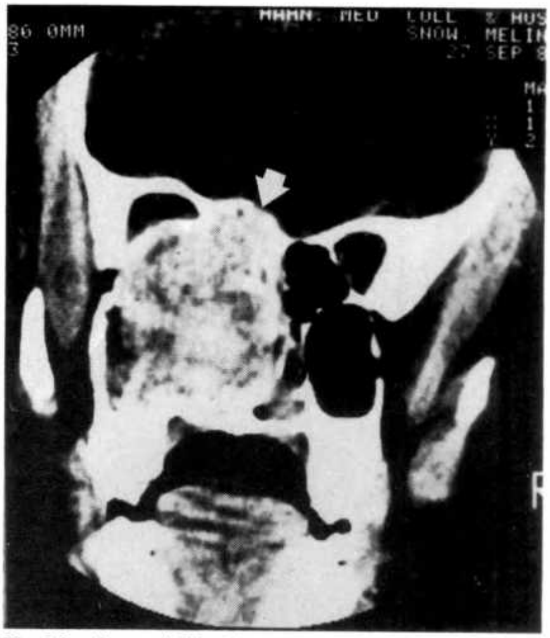

Fig. 2C *Coronal CT without contrast material at the level of the posterior orbits. (Note that the patient's left side corresponds with the reader's in the coronal view.) The large mass fills the left maxillary and ethmoid sinuses, the left nasal cavity, and has invaded the infrafrontal intracranial epidural space (arrow). The heterogeneous density of the lesion, with many foci of calcification and/or ossification, is well shown. The mass has bowed the left orbital floor superiorly.*

PATHOLOGICAL FINDINGS

The specimen consisted of several pieces of rather gritty, tan-brown tissue ranging in size from 11×8×3·5 cm to 0·4×0·2×0·2 cm. Histological sections showed it to consist of a cellular, fibroblastic stroma containing spindle-shaped cells and numerous osseous spicules. A few giant cells were present adjacent to the bony spicules. On higher-power

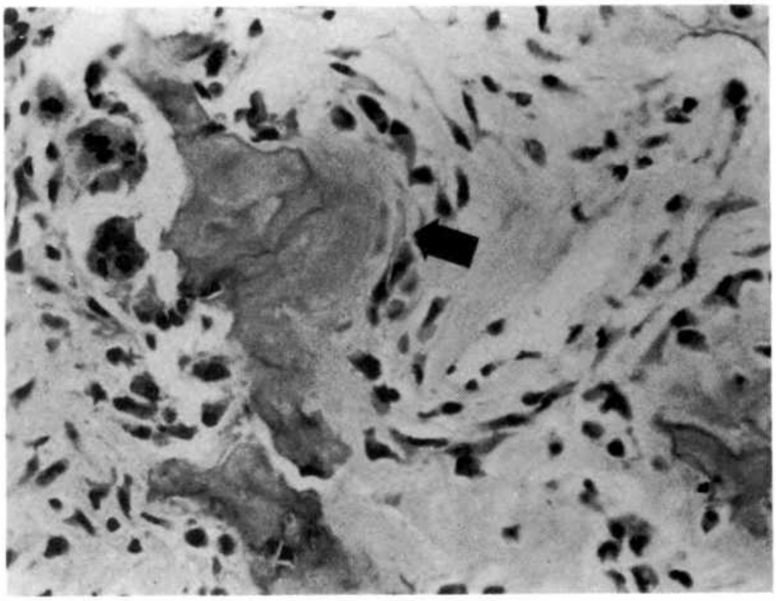

Fig. 3 *Photomicrograph showing spicules of bone (arrow) with surrounding osteoid and a rim of osteoblasts around the osteoid material outside the bony spicules. A giant cell is present adjacent to the bony spicule. (Haematoxylin and eosin, × 67).*

microscopy it was noted that the bony trabeculae were lined by lightly eosinophilic material, suggestive of osteoid, which was in turn rimmed by osteoblasts (Fig. 3). These findings were compatible with the diagnosis of ossifying fibroma of bone.

Discussion

The classification of fibro-osseous tumours, particularly those in the orbital region, has been the subject of some controversy.[1 2] Blodi has stated that ossifying fibromas in the cranial region might be regarded as a variant of fibrous dysplasia.[1] Other authorities have expressed the opinion that ossifying fibromas should be grouped as a variant under the more general category of osteoblastomas.[2] More recently other authors have believed that the histopathological findings are sufficient to classify ossifying fibromas into a separate category.[3-9] A recent report has delineated the clinical, histopathological, and computed tomographic characteristics which help in the diagnosis of juvenile ossifying fibroma.[4] The CT finding of a well circumscribed tumour with patchy areas of sclerosis within the matrix of the lesion strongly suggested the diagnosis of ossifying fibroma in the case reported here. Margo and associates recently reviewed the cases of ossifying fibromas with orbital involvement from the files of the Armed Forces Institute of Pathology.[5] Among 21 cases on file 10 lesions were centred in the orbital plate of the frontal bone, nine in the ethmoid sinus, and in two cases the precise location was not determined. These tumours characteristically produced downward or lateral displacement of the globe. Our patient was particularly unusual in that the tumour produced proptosis and upward displacement of the globe, indicating its origin in the maxillary sinus. Ossifying fibroma of the maxillary sinus should be considered in the differential diagnosis when a child or young adult presents with proptosis and slowly progressive upward displacement of the globe.

Although ossifying fibroma is generally believed to be difficult to diagnose histopathologically, Margo and associates have recently presented a detailed account of the rather distinctive features of this tumour as seen by light and electron microscopy.[5] The numerous rounded, mineralised collagenous foci, which they termed 'psammomatoid ossicles,' were the basis for their favouring the term 'psammomatoid ossifying fibroma.'

It is currently believed that the best management of juvenile ossifying fibromas is surgical excision. Because these tumours can recur after incomplete excision,[5] every attempt should be made to remove the mass completely. In most cases this must be accomplished piecemeal to remove as much of the mass as possible while protecting adjacent vital and cosmetically important structures. The surgical approach should be determined by the location and size of the tumour as indicated by CT. Computed tomography is also invaluable in the postoperative follow-up to detect recurrence of the tumour.

Although the pathogenesis of juvenile ossifying fibroma is unknown, it appears to be a spontaneously

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occurring benign neoplasm of bone, which most commonly becomes clinically apparent in children and young adults between the ages of 6 and 21 years.[5] We believe that clinical awareness of this tumour, combined with further refinement of its CT features, will lead to more accurate clinical diagnosis and more effective management of patients with juvenile ossifying fibromas in the orbital region.

The patient was also evaluated clinically by Dr Lois Martyn. Mr David Silva also provided assistance.

This work was supported in part by the Pennsylvania Lions Sight Conservation and Eye Research Foundation, Inc., the Ocular Oncology Fund, and the Oncology Research Fund, Wills Eye Hospital, Philadelphia, USA.

References

1 Blodi FC. Pathology of the orbital bones. The XXXII Edward Jackson Memorial Lecture. *Am J Ophthalmol* 1976; **81:** 1–26.

2 Henderson JW. *Orbital tumors.* 2nd ed. New York: Decker, 1980: 205–8, 225–31.

3 Jones IS, Jakobiec FJ, eds. *Diseases of the orbit.* Hagerstown: Harper and Row, 1979: 483–502.

4 Shields JA, Nelson LB, Brown JF, Dolinskas C. Clinical, computed tomographic, and histopathologic characteristics of juvenile ossifying fibroma with orbital involvement. *Am J Ophthalmol* 1983; **96:** 650–3.

5 Margo CE, Ragsdale BD, Perman KI, Zimmerman LE, Sweet DE. Psammomatoid (juvenile) ossifying fibroma of the orbit. *Ophthalmology (Rochester)* in press.

6 Dahlin DC. *Bone tumors. General aspects and data on 621 cases.* Springfield: Thomas, 1978: 362–9.

7 Scott M, Peale AR, Croissant PD. Intracranial midline anterior fossae ossifying fibroma invading orbits, paranasal sinuses, and right maxillary antrum. *J Neurosurg* 1971; **34:** 827–31.

8 Kahlil MK, Leib ML. Cemento-ossifying fibroma of the orbit. *Can J Ophthalmol* 1979; **14:** 195–200.

9 Fu YS, Perzin KH. Non-epithelial tumors of the nasal cavity, paranasal sinuses, and nasopharynx. A clinicopathologic study. II. Osseous and fibro-osseous lesions, including osteoma, fibrous dysplasia, ossifying fibroma, osteoblastoma giant cell tumor, and osteosarcoma. *Cancer* 1974; **33:** 1289–305.

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Correspondence

Leber's congenital amaurosis

SIR, Chew, Deutman, Pinckers, and Aan de Kerk recently reported a case of Leber's congenital amaurosis with the uncommon fundus variant of 'marbilised fundus,'[1] in which the age of onset of the fundus lesions was unknown. The authors cited two previous reports from the literature in which similar fundus lesions were found at age 21 months and 4 years with histories of previously normal fundi.

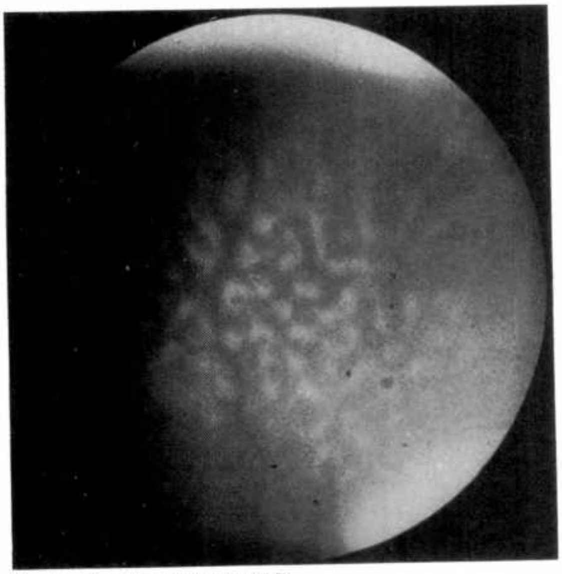

Fig. 1 *Peripheral fundus OD.*

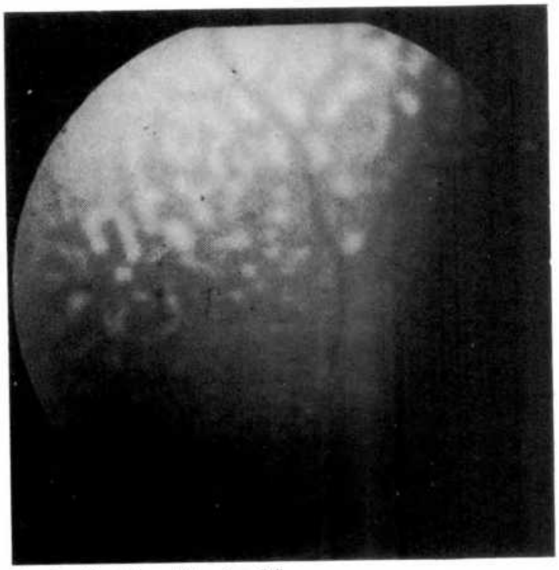

Fig. 2 *Peripheral fundus OS.*

We have had occasion to see a similar case, first in 1974 when the patient, a black female with no apparent vision but otherwise well, was 6 months old. At that time dilated fundus examination under anaesthesia (EUA) was normal. Repeat EUA in 1977 at age 4 years revealed bilateral peripheral fundus lesions essentially identical to those described by Chew *et al.* (Figs. 1, 2), along with bilaterally unrecordable ERGs and flash VERs.

Our case provides further evidence that this fundus variant of Leber's amaurosis develops between 6 months and 2 years of age.

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H SKALKA

Reference

1 Chew E, Deutman A, Pinckers A, Aan de Kerk A. Yellowish flecks in Leber's congenital amaurosis. *Br J Ophthalmol* 1984; **68:** 77-31.

Book review

My First Library: Sight. By JILL BENNETT AND ROGER SMITH. Pp. 29. £3·50. Macdonald: London. 1984.

This is one of a series of educational books under the series My First Library. Written for children, these educational books give a simple explanation of various aspects of our lives—for example, others in the series are on computers, homes around the world, and several other themes.

Sight is well illustrated throughout in colour photographs and drawings, the balance between the two being carefully considered. It is often more effective for children to have a simple colour illustration, and the authors have used these with great effect. A general introduction to seeing is followed by simple explanations of the eyes' function, focusing, eye protection, binocular vision, and simple experiments such as locating the blind spot and physiological diplopia. Blindness is covered in a simple, factual, unalarmist manner emphasising the positive aspects such as Stevie Wonder's success as a musician.

This is an excellent book for children and a must for all children's libraries, and it would make an excellent present for any inquisitive child. JAMES L KENNERLEY BANKES

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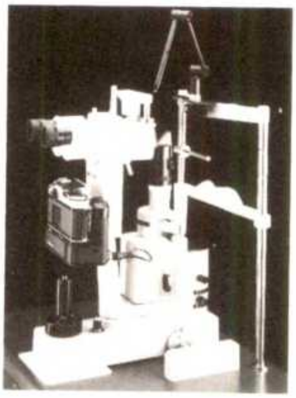

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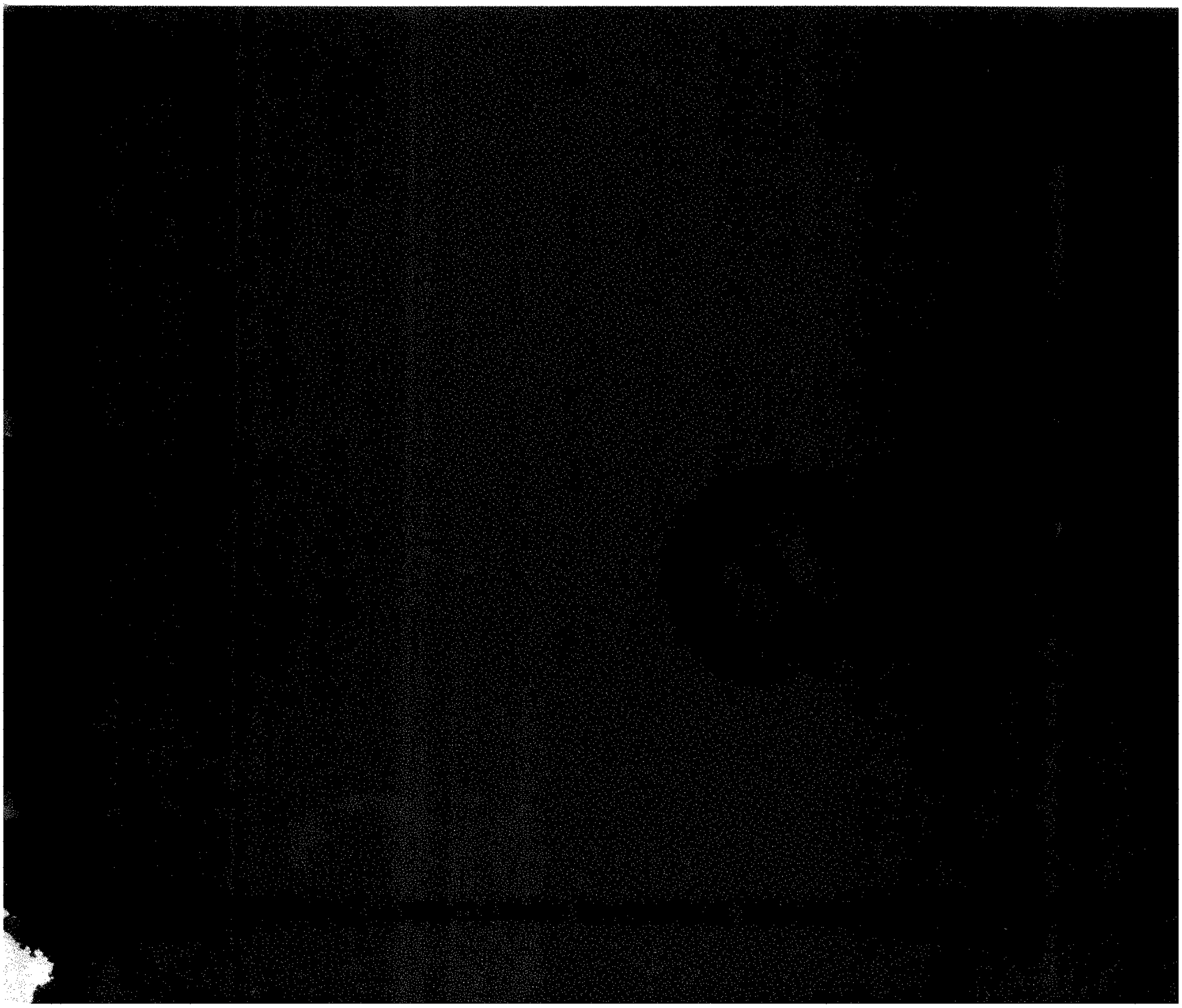

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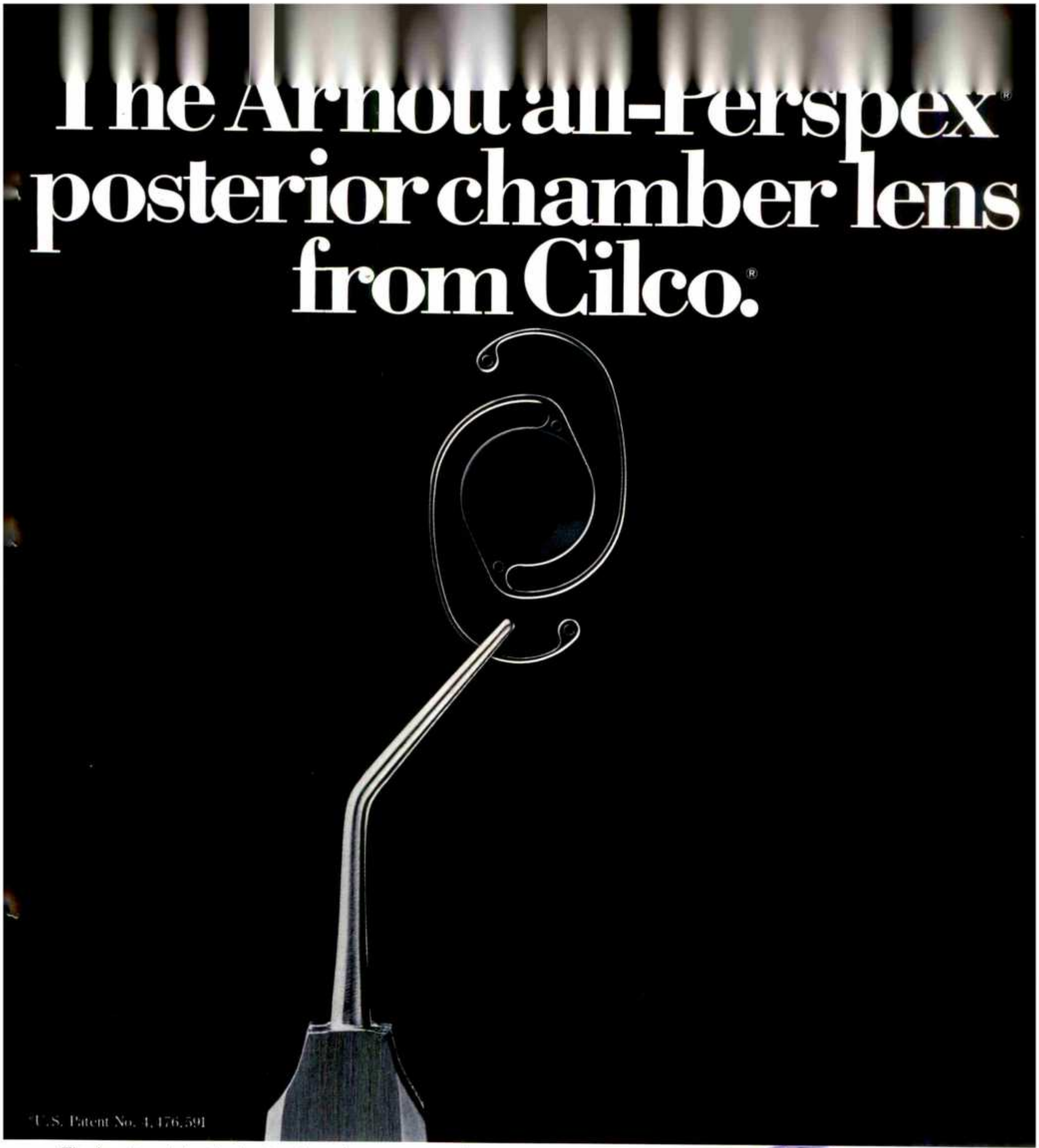

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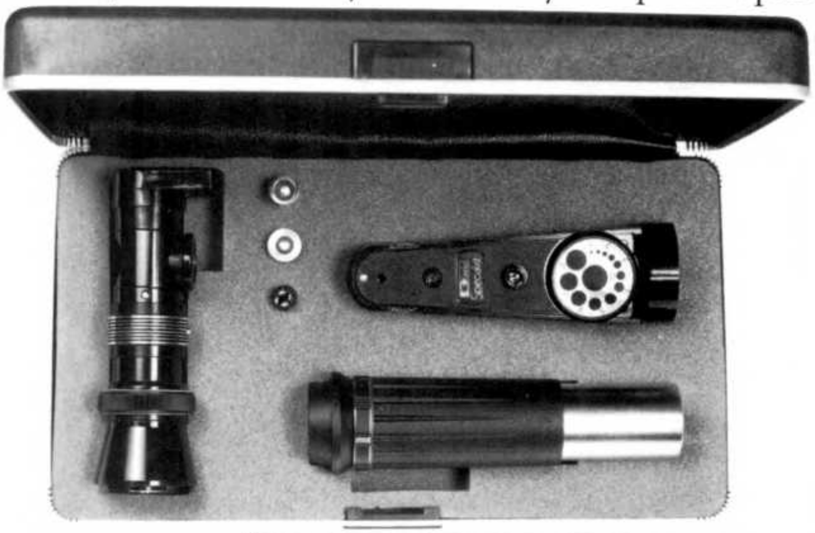

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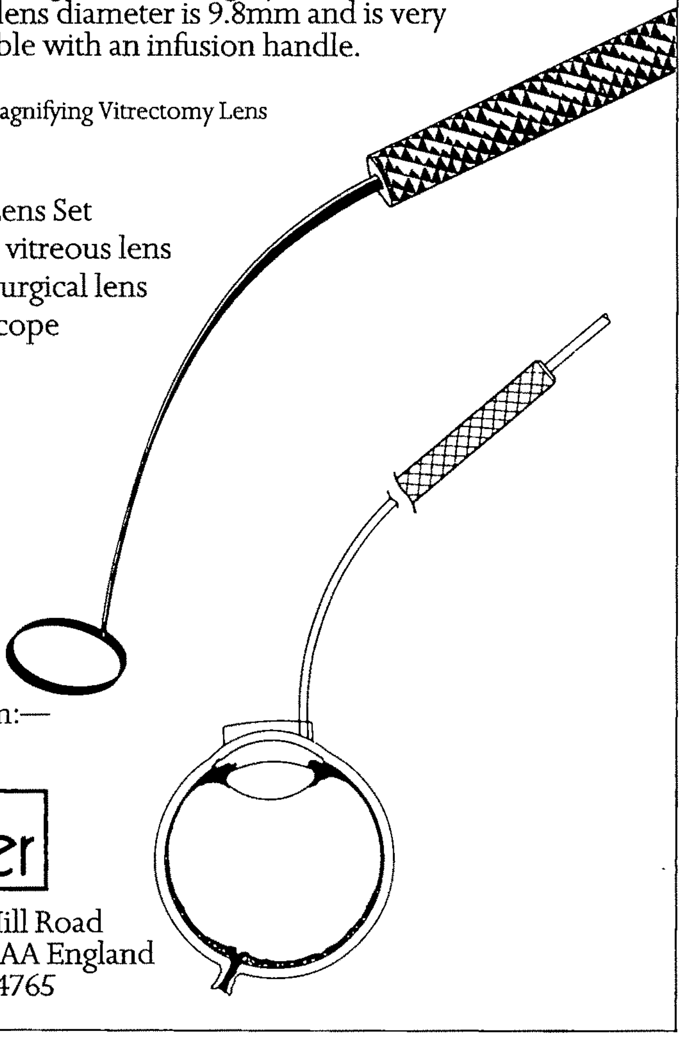

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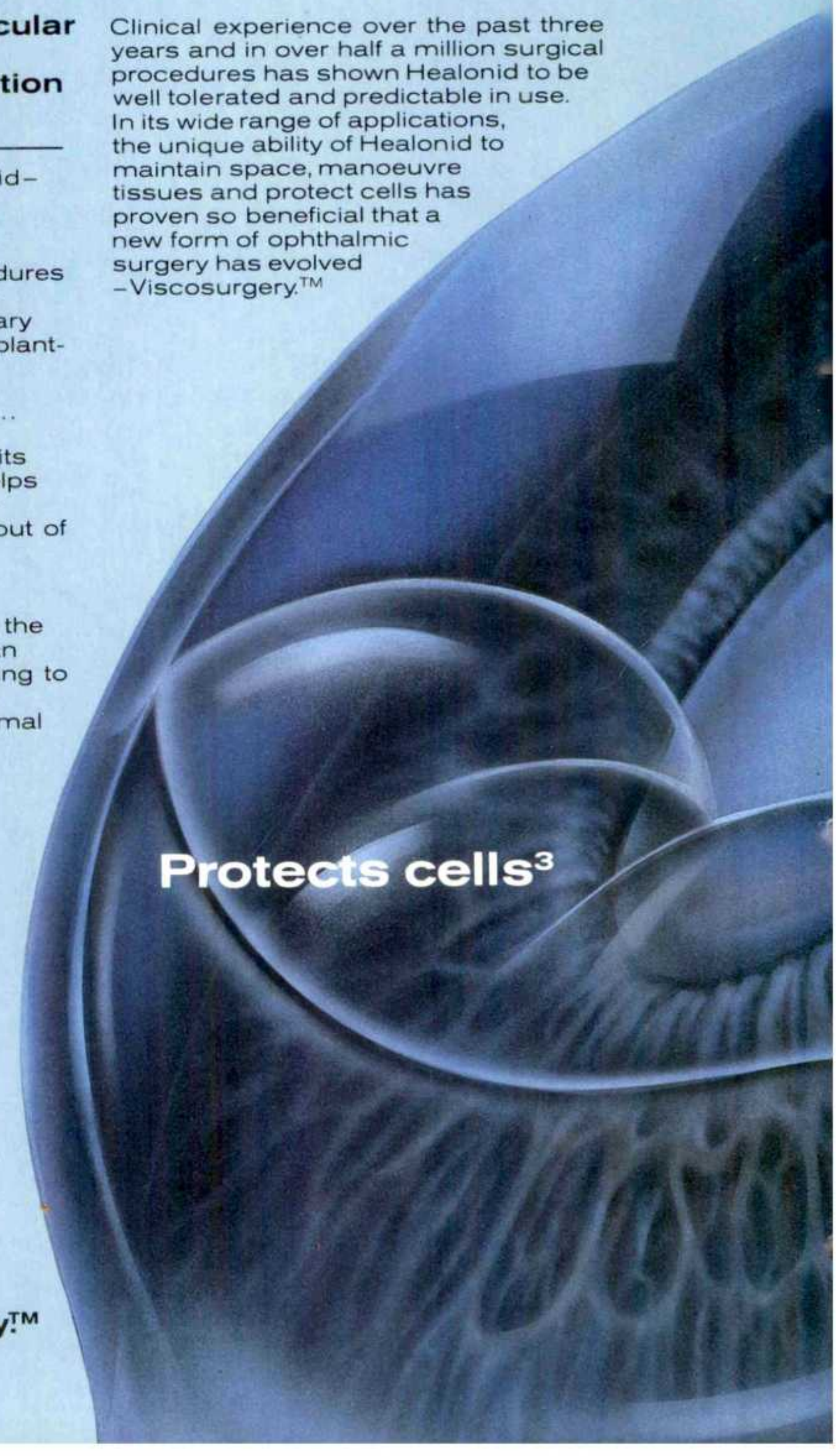

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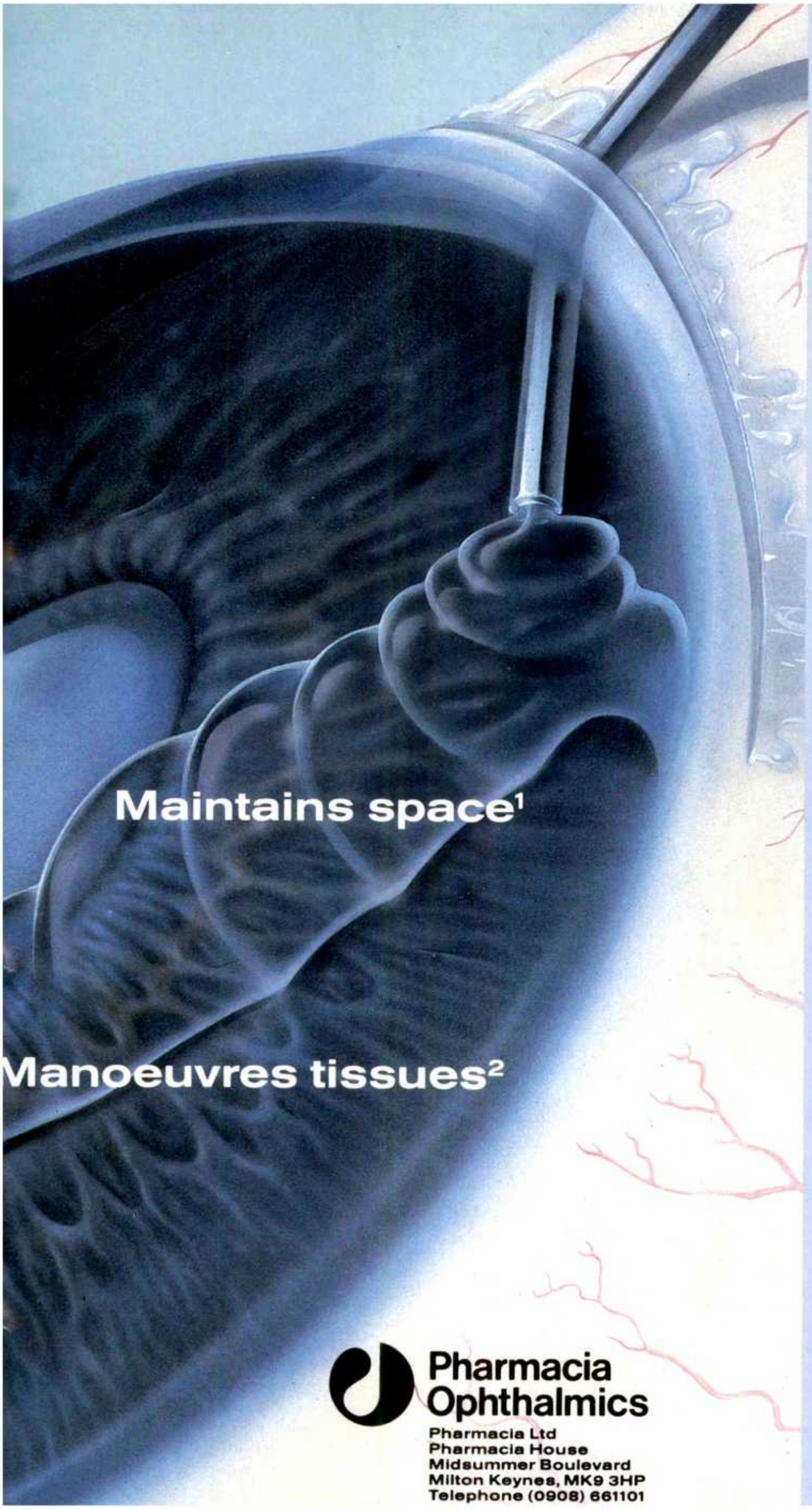

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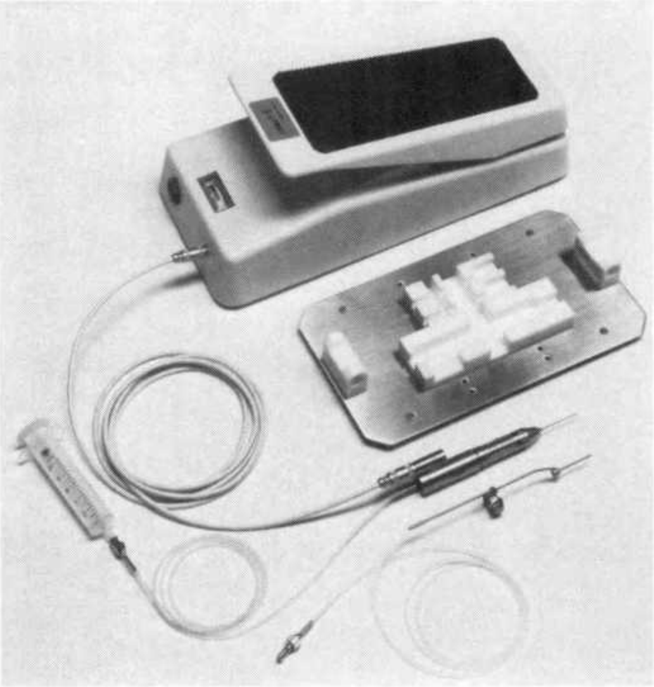

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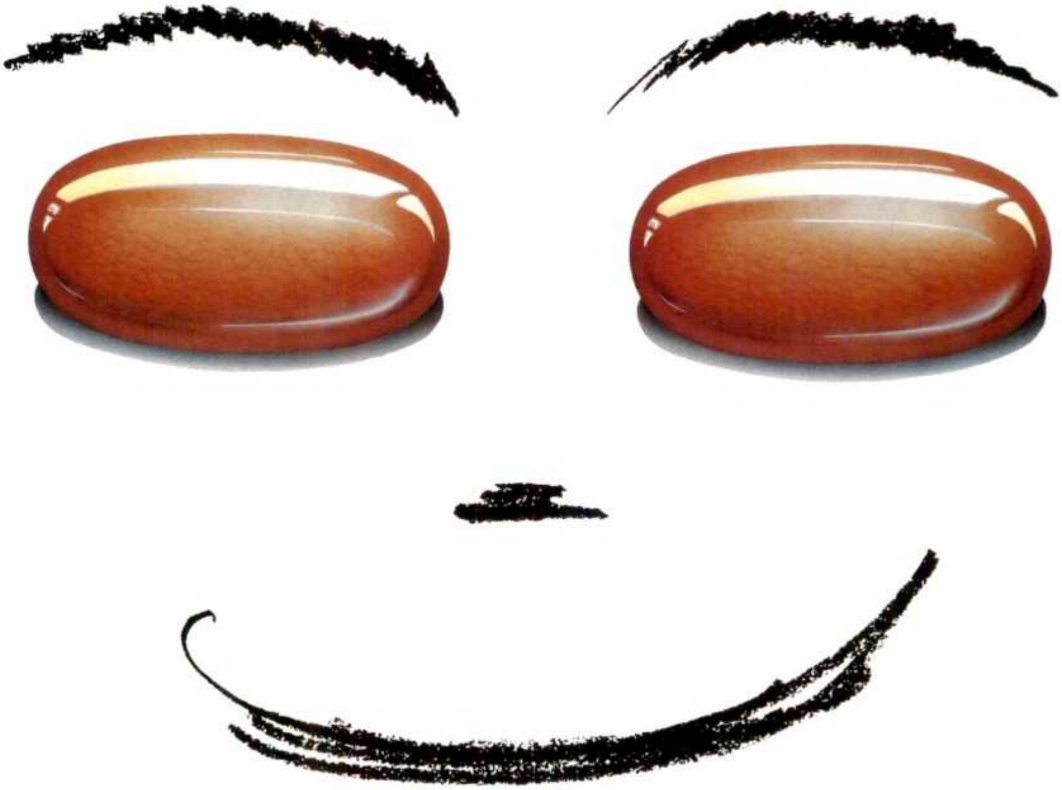

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References:
1. Garner LL, et al, Amer. J. Ophthalmol. 1963 **55,** 323-327.
2. Duke Elder, WS, Textbook of Ophthalmology as quoted in: Moses, RA, Adlers Physiology of the Eye, 1975: 192.

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British Journal of Ophthalmology, 1985, **69**, 397–403

Retinal pigment epithelial detachments in the elderly: classification and outcome

A G CASSWELL, D KOHEN, AND A C BIRD
From Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY Sixty-four eyes of 57 elderly patients with pigment epithelial detachments (PEDs) were studied with the aim of describing their morphological features and identifying prognostic factors. They were classified into four groups according to the following characteristics: *(a)* early fluorescence, *(b)* late fluorescence, *(c)* shallow detachment with limited fluorescence ('drusen type'), *(d)* irregular fluorescence. The following conclusions were drawn: (1) 30% developed demonstrable subretinal new vessels; all groups except the drusen type were susceptible, the irregular group being particularly prone. (2) 10% developed retinal pigment epithelial tears, and these occurred almost exclusively in the slow fluorescent group. (3) Flattening of PEDs was a feature of drusen type and early fluorescent groups. (4) Most patients lost vision. RPE tears occurred within a few months of presentation with immediate loss of vision; likewise rapid loss of vision followed the development of demonstrable new vessels, though not necessarily in those with changes thought to imply the presence of new vessels. Flattening after prolonged detachment was associated with pigment epithelial atrophy and invariable loss of vision. Visual acuity was maintained consistently only in those eyes with persistent detachment.

Pigment epithelial detachments (PEDs) are discrete, serous elevations of the retinal pigment epithelium. During fluorescein angiography the subpigment epithelial space fills progressively with dye and remains hyperfluorescent long after dye transit.[1] Recent behavioural studies have shown that the visual prognosis may be determined by the size of the lesion and the age of the patient. Lewis[2] has shown that in younger patients (less than 55 years old) the visual prognosis is good. Meredith *et al.*[3] found that elderly patients with small PEDs have a relatively better visual prognosis than those with large lesions but identified no other features as useful indicators of prognosis.

PEDs have a complex variety of appearances. The nature of the different characteristics and the significance of particular changes to visual prognosis have not been defined. In particular it is acknowledged that the exclusion of subretinal new vessels can be difficult, so that it may be impossible to be sure that a lesion is 'avascular.' It has been considered that their presence may be implied by the presence of focal hyperfluorescent spots within a PED, yellow subretinal deposits, and turbid fluid.

In the past it has been thought that PEDs caused subretinal new vessels to develop and that this complication represented the principal threat to vision. Photocoagulation has been used to flatten the pigment epithelium with the aim of restoring vision and preventing the development of disciform lesions, but a recent controlled trial of elderly patients treated with argon laser photocoagulation implies that this form of therapy confers no visual benefit.[4] During this trial sight threatening complications other than the development of subretinal new vessels were identified.

It was the results of the trial and the observations made during the study which stimulated the present review to classify the morphological features of PEDs and to identify whether any particular characteristics had prognostic significance. Information of this type may help in identifying the expectations for vision in a patient and would also contribute to planning any further trials of treatment for PEDs.

Correspondence to Mr A G Casswell, FRCS.

Material and methods

We undertook a retrospective study of 64 consecutive untreated patients older than 55 years with pigment epithelial detachments who were referred to the Retinal Diagnostic Department at Moorfields Eye Hospital from 1976 to 1981.

The criteria for the diagnosis of a PED was elevation of the retinal pigment epithelium with accumulation of fluorescein dye in the subpigment epithelial space during angiography. Patients with identifiable subretinal new vessels, subretinal haemorrhage, unexplained focal hyperfluorescent spots, or extensive subretinal exudates were excluded. Those patients with high myopia and any additional past or present eye disease which could affect the visual acuity were also excluded.

The following were recorded: the age and sex of the patient, duration of symptoms, corrected visual acuity, signs of age related macular changes (drusen etc.), the size, location, and ophthalmoscopic features of the PEDs, together with the pattern of fluorescence during angiography. At follow-up visits the visual acuity was recorded and colour photographs and fluorescein angiography were repeated.

In the first part of the study we classified foveal and juxtafoveal PEDs on the basis of their ophthalmoscopic and fluorescein appearances. In the second part we recorded the outcome and visual acuity of all PEDs that had been observed for at least one year, or less if they developed a sight losing complication within that time. All those patients who did not have adequate follow-up were requested to attend again.

The diagnosis of a disciform lesion was based on the demonstration of new vessels or the presence of subretinal haemorrhage in the absence of a tear of the retinal pigment epithelium (RPE). The development of yellow subretinal exudates and the delayed appearance of fluorescence was not regarded as diagnostic of subretinal neovascularisation.

Results

CLASSIFICATION

We classified 64 PEDs of 57 patients into four groups based on the fundal appearance and fluorescein angiograms.

Hyperpigmentation of the pigment epithelium (pigment figure) was a feature of many lesions and was not used to differentiate one group from another. In several lesions a patch of hypofluorescence was identified which appeared to be due to obstruction of fluorescein at the level of the pigment epithelium without any corresponding lesions seen by ophthalmoscopy (Fig. 1).

1. Early hyperfluorescent group (17 eyes). A discrete dome-shaped elevation of the RPE is seen ophthalmoscopically. During fluorescein angiography the subpigment epithelial space fluoresces early and progresses to an even hyperfluorescence in the later stages of the transit (Figs. 1, 2). This appearance may be modified by small areas of

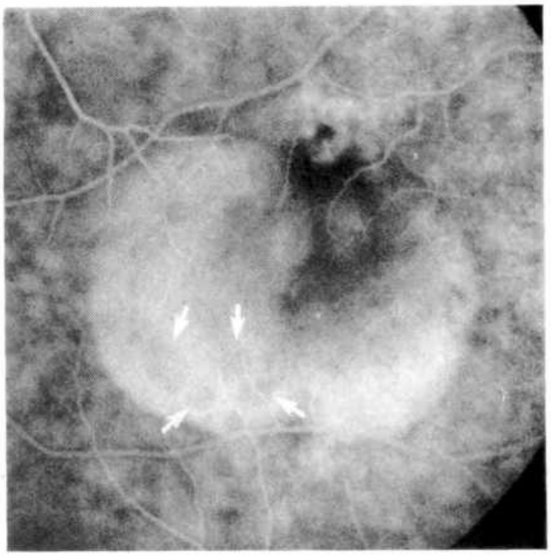

Fig. 1 *Fluorescein angiography of a pigment epithelial detachment showing hypofluorescent patches in its lower part (arrows). No ophthalmoscopic abnormalities were found to correspond with these.*

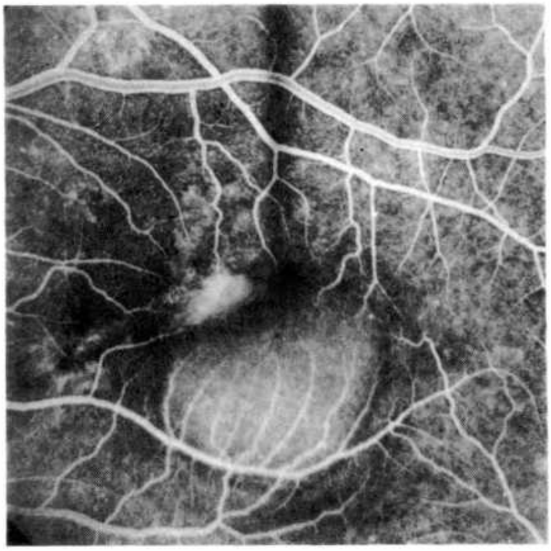

Fig. 2 *Fluorescein angiography of a pigment epithelial detachment filling early in the angiogram with even hyperfluorescence.*

hyperfluorescence which can be identified as corresponding to areas of pigment epithelial atrophy or drusen that have become detached with the pigment epithelium or occasionally round well-defined zones of hypofluorescence that have no corresponding feature ophthalmoscopically.

2. *Late fluorescing group* (14 eyes). Ophthalmoscopically these cannot be differentiated from the early hyperfluorescent PEDs. They are characterised by the appearance of fluorescence after the arteriovenous phase (delayed appearance), which progresses slowly to an even and featureless hyperfluorescence (Figs. 3, 4). In some cases fluorescence may appear first at the edges of the PED and spread concentrically inwards.

3. *Drusen type* (18 eyes). Multiple large confluent drusen are seen in and surrounding these PEDs, which are usually shallow and irregular in outline. On fluorescein angiography they fluoresce faintly during the transit and do not progress to the bright hyperfluorescence seen in the lesions of other groups (Fig. 5). The presence of underlying drusen modified the angiographic appearance of the lesion in that at the site of the drusen the fluorescence was less marked than elsewhere in the lesion.

4. *Irregular fluorescence* (10 eyes). Though ophthalmoscopically indistinguishable from the first two groups, angiography reveals an overall fine irregularity of fluorescence. Typically the irregularity of fluorescence comprises multiple areas of hypo- and hyperfluorescence over the whole detachment. The hyperfluorescent areas increase in fluorescence during the study, whereas the hypofluorescent areas remain unchanged (Fig. 6).

5. *Mixed group* (5 eyes). There were five PEDs with two zones of different characteristics during angiography, usually one area of irregular fluorescence adjacent to a slowly filling hyperfluorescent area. Typically the half with slow fluorescence was the more elevated of the two.

Other characteristics did not serve to differentiate between groups, the average age, age ranges, and presenting visual acuities being similar (Table 1). Although size was variable within each group, there was a tendency for the Drusen PEDs to be smaller (0·96 disc diameters, Fig. 5) and for the slowly filling PEDs to be larger (2·1 disc diameters, Fig. 4).

OUTCOME

Morphological

A variety of changes were identified during the period of review (Table 2). With few exceptions spontaneous flattening occurred only after an interval of several years. In many there was persistence of the PED, though the characteristics changed in some. One drusen PED enlarged and became rapidly fluorescent, and several PEDs became irregularly fluorescent before either flattening or developing new vessels. In four eyes subretinal exudates developed round the margins of the detachment without demonstrable subretinal new vessels at any stage. In 30% a disciform lesion developed. In 10%

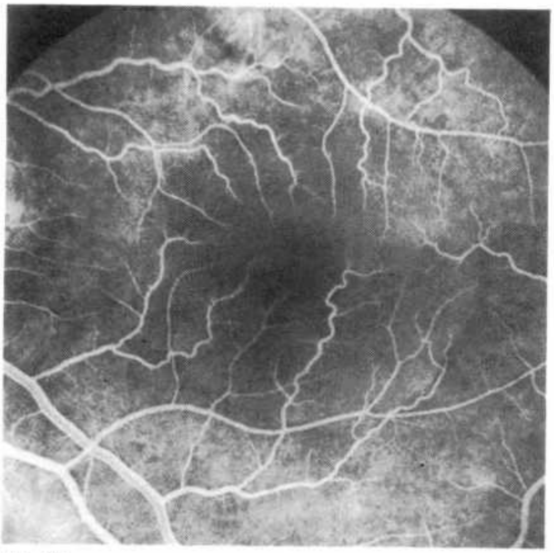

Fig. 3A

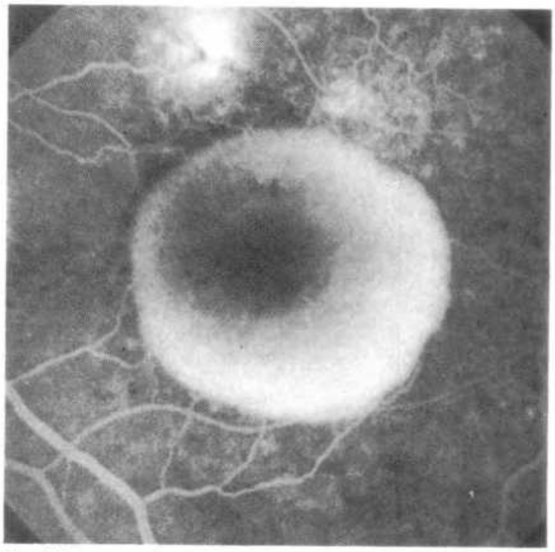

Fig. 3B

Fig. 3 *Fluorescein angiography of a pigment epithelial detachment in the posterior pole showing slow development of hyperfluorescence, which is uniform.*

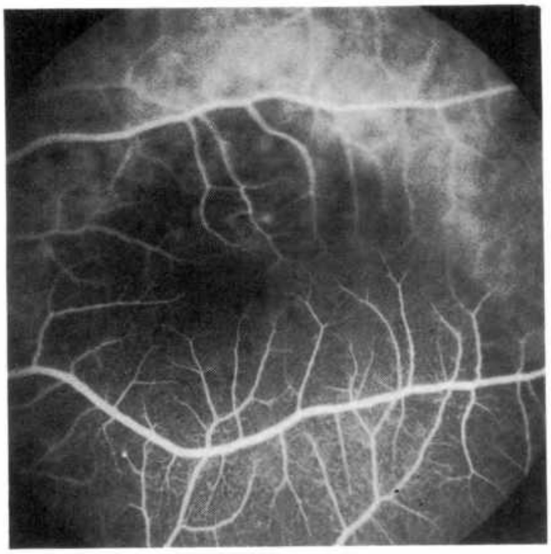

Fig. 4A

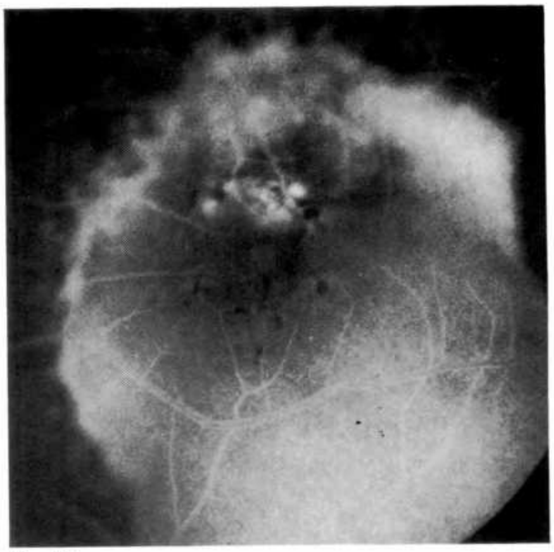

Fig. 4B

Fig. 4 *Fluorescein angiography of a large pigment epithelial detachment showing slow acquisition of hyperfluorescence, which is uniform.*

there was a tear of the pigment epithelium, and in each case this occurred within a few months of presentation. The true figure is probably higher than 10%, as some patients presented with this early complication and were excluded from the review.

The characteristics of the lesion when the patient was first seen were not an absolute determinant of subsequent behaviour, but certain complications were clearly more common in some types than others (Table 2). Subretinal neovascularisation was much more common in those with fine irregular hyperfluorescence than in others, though this process became evident in all types except the shallow 'drusen detachments.' All but one of the tears occurred in 'slow hyperfluorescent' lesions.

Visual

The visual outcome was also correlated to some extent with the initial classification. The irregular and slow fluorescent PEDs had worse final vision than the other types, and the shallow drusen types fared best of the groups.

As might have been predicted, the final visual acuity was poor in those patients who developed tears of the retinal pigment epithelium or subretinal new vessels (Table 3). The visual outcome was also bad in those lesions in which there was spontaneous flattening of the pigment epithelium. The only lesions associated with consistently good vision at the end of the review period were those with persistent detachment.

Discussion

INTERPRETATION OF APPEARANCE

Certain determinants of behaviour of PEDs during fluorescein angiography might be predicted on the basis of theoretical considerations together with the limited knowledge of the structural changes occurring within the lesion derived from histopathological studies. It is generally assumed that the hyperfluorescence of PEDs is due to the increased thickness of the fluorescing medium due to dye accumulation in the subpigment epithelial space, the fluorescein being derived from the choroid having passed into subretinal space by diffusion through Bruch's membrane. Unequal rates of dye accumulation might be predicted if there were variation of the lipid content within Bruch's membrane or the subepithelial fluid from one lesion to another or within a single lesion. This would influence the speed of diffusion, since fluorescein-sodium is highly soluble in water but not in lipid. It is well recognised that material accumulating within and on the inner surface of Bruch's membrane with age contains both lipid and protein, but the results of a systematic analysis of this material in man do not exist.

The appearance of fluorescence may also be modified by the transparency of the subpigment epithelial fluid and the detached structures; this is well illustrated by the light absorption by luteal pigment and pigment figures. Clinical evidence implies that pigment epithelium may become detached, with drusen

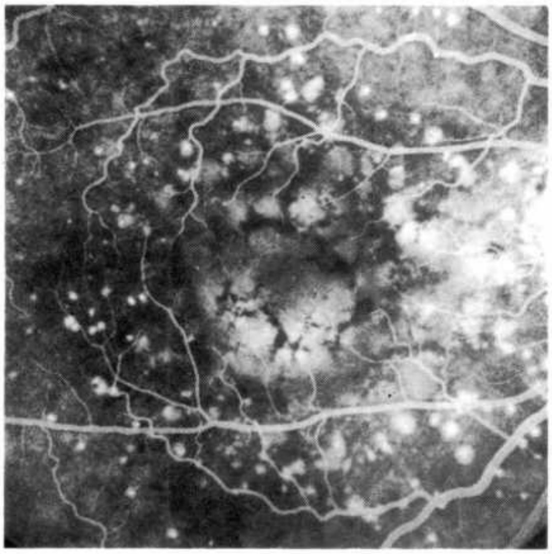

Fig. 5 *Fluorescein angiography of a shallow pigment epithelial detachment associated with drusen.*

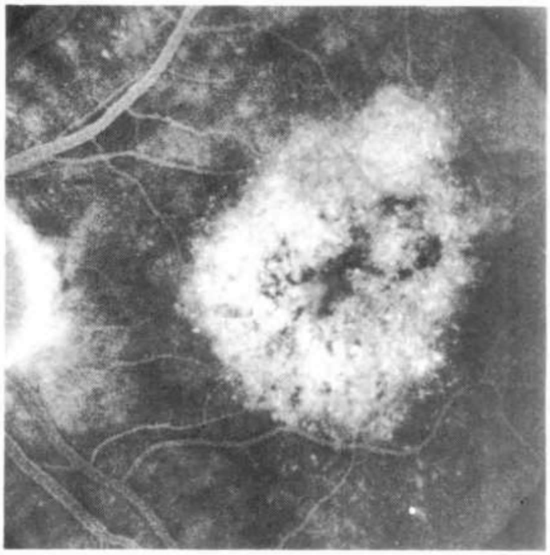

Fig. 6 *Fluorescein angiography of a pigment epithelial detachment with irregular hyperfluorescence.*

on its under surface in some lesions but not in others. That there should be a similar disparity in the behaviour of pigment epithelial basement membrane has been postulated by Hoskin *et al.*[5] Such variation in the distribution of material would predictably influence the appearance of the lesion clinically and during angiography, and this could account for the two different zones of a 'mixed PED.'

The slow appearance of fluorescence in some lesions may be accounted for by slow diffusion of dye into the subretinal space due to high lipid content within the subpigment epithelial fluid or in Bruch's membrane, or by the presence of blue/green absorbing material within the subpigment epithelial fluid, so that fluorescence is not recorded until the dye has diffused as far as the detached pigment epithelium. The latter would explain the appearance of fluorescein at the periphery of the lesion in the early stages of the study, a feature common to many lesions. These two situations may coexist, since lipofuscin, which absorbs blue light well, is the most likely lipid to accumulate at these sites. By contrast in those PEDs which become rapidly and evenly fluorescent it is unlikely that there is a high lipid content within either Bruch's membrane or the subretinal fluid or that the detached tissues contain large amounts of blue/green absorbing pigments.

The diffuse irregular fluorescence in the irregular masking group suggests irregular transmission of light by the detached tissues due to material on the outer aspect of the detached retinal pigment epithelium. While the origin of such a material is unknown, it could result from deposition of phagosomal debris, thickening of pigment epithelial basement membrane, or possibly the product of undetected new vessels.

The focal and increasing fluorescence which corresponds with large drusen seen on the undersurface of Bruch's membrane is probably due to displacement of pigment within the detached pigment epithelium and accumulation of dye in the drusen. The areas of hypofluorescence seen without

Table 1 *Pigment epithelial detachments at presentation*

Type	*No.*	*Age*		*Size*	*VA (worse than 6/24)*	*VA (mean)*
		Mean	*Range*			
Early	17	65·70	(56–75)	1·90	3	6/12
Late	14	69·9	(57–79)	2·10	1	6/12
'Drusen'	18	65·3	(57–78)	0·96	0	6/12
Irregular	10	67·27	(64–79)	1·70	1	6/12
Mixed	5	70	(67–74)	2·45	0	6/12

Size measured in disc diameters.

Table 2 *Outcome of pigment epithelial detachments with a follow-up of one year or more*

Type	*No.*	*Outcome*				*VA (worse than 6/24)*	*VA (mean)*
		Flat	*PED*	*Disc*	*Tear*		
Typical	16	3	6	6	1	9	6/24
Late	11	0	4	3	4	5	6/36
'Drusen'	15	6	9	0	0	5	6/12
Irregular	8	0	2	6	0	4	6/48
Mixed	3	0	0	2	1	1	6/36

Flat=PEDs that spontaneously flatten.
PED=pigment epithelium remaining detached.
Disc=development of a disciform lesion.
Tear=pigment epithelial tear.

Table 3 *Visual change of PEDs in terms of their outcome*

Outcome	*No.*	*Age*	*Size (DD)*	*Initial VA (mean)*	*Follow-up (months)*	*Final VA (mean)*	*Worse than 6/24*
Flat	9	64	1·5	6/13	49	6/30	7
PED	21	65·1	1·23	6/10	29·5	6/15	4
Disciform	15	67·4	2·25	6/13	14·5	6/24	8
Tears	6	70	3·04	6/21	7	6/36	4

Follow-up=mean time between presentation and event. DD=disc diameter.

corresponding ophthalmoscopic changes appear to be due to transmission change at the level of the pigment epithelium, which might be caused by accumulation of a blue/green absorbing pigment other than melanin, which may be intra- or extracellular. Collections of lipofuscin-containing macrophages or RPE cells growing on the outer surface of the detached RPE would account for such an appearance.

Drusen PEDs are small, shallow, and surrounded by and containing large drusen. The large drusen contained within the PED fluoresce faintly towards the end of the transit, and because they occupy most of the sub-RPE space there is relatively little sub-RPE fluid to accumulate fluorescein, thus limiting fluorescence. The difficulty differentiating some of these ophthalmoscopically from confluent drusen suggests that they may develop as a direct result of accumulation of confluent drusen rather than indicating the onset of a new process.

OUTCOME

If the variation in the appearance of retinal pigment epithelial detachments is due to different distribution of cellular and non-cellular material within the lesion, correlation might be expected between the clinical characteristics of the lesion and its subsequent behaviour.

Hoskin has postulated that the features of 'slow filling' lesions implied that the retinal pigment epithelium may be detached without a normal basement membrane and that the lack of physical support within the detached tissue would increase the risk of tearing. The results of this study support the conclusion concerning the risk of this complication occurring in this type of lesion, though the conclusions concerning pathogenesis have not been tested. The larger size of these lesions may also be important in the pathogenesis of the tear. While disciform lesions occurred within this group, four patients had no evidence of subretinal new vessels at the end of the review period. This means that turbidity of the subpigment epithelial fluid does not necessarily imply the inevitable presence of neovascularisation. It is clear, however, that in such cases new vessels may have been present on the inner surface of Bruch's membrane when the patient was first seen and may not have been identified on angiography. This phenomenon has been identified in the past,[4] and it was shown that blood vessels at this level may not involve the detached pigment epithelium and do not necessarily cause loss of visual acuity.

Disciform lesions were common in the lesions with finely irregular hyperfluorescence. This may be related to the presence of debris on the under surface of the detached tissues, which may stimulate neovascularisation and in particular cause the new vessels to grow at the level of the pigment epithelium rather on the inner surface of Bruch's membrane.

Few sight threatening complications were seen in the 'drusen RPE detachments.' This may be a consequence of their small size and the shallow detachment; there is little evidence that the large drusen would suppress the development of new vessels.

It was not surprising that severe visual loss was common in patients with tears of the retinal pigment epithelium or vascular disciform lesions. However, the explanation for the poor vision in those lesions which flattened spontaneously is not evident. It is possible that flattening caused function to be lost or that tissue failure caused both the loss of vision and the resolution of the detachment, the second explanation being the most attractive of the two.

Some useful prognostic information can be gained from the morphological appearance of PEDs. PEDs of all groups except the drusen group are at risk of developing disciform lesions, and those with irregular fluorescence were the worst affected. Nearly all the RPE tears were in the slow fluorescing group. The visual prognosis is poor for all groups. RPE tears are followed by visual loss within days of occurrence. The development of new vessels was accompanied by visual loss within a few months, and those that flattened after several years had atrophy of the RPE and visual loss. These results should be useful in the planning of any future trial of the treatment of pigment epithelial detachments.

References

1 Donald J, Gass M. Pathogenesis of disciform detachment of the neuroepithelium. *Am J Ophthalmol* 1976; **63:** 617–44.

2 Lewis ML. Idiopathic serous detachment of the pigment epithelium. *Arch Ophthalmol* 1978; **96:** 620–4.

3 Meredith TA, Braley RE, Aaberg TM. Natural history of serous detachments of the retinal pigment epithelium. *Am J Ophthalmol* 1979; **88:** 643–51.

4 Moorfields Macular Study Group. Retinal pigment epithelial detachments in the elderly: a controlled trial of laser. *Br J Ophthalmol* 1982; **66:** 1–16.

5 Hoskin A, Bird AC, Schmi K. Tears of the detached retinal pigment epithelium. *Br J Ophthalmol* 1981; **65:** 417–22.

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Rod-cone interactions and analysis of retinal disease

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SUMMARY Cone flicker threshold rises as the rods dark adapt, though the cone threshold to continuous light remains constant. The rise is normally about 1 log unit, but in certain patients who complain of night blindness it may be as great as 2·5 log units. In these persons the kinetics of the rod-cone interaction are those of the recovery of rod sensitivity. The rods impose a low-pass filter on the cones. This effect is absent in congenital nyctalopia and X-linked retinoschisis. We suggest that cone flicker is maintained through a feedback system involving horizontal cells, and when the rod dark current returns in dark adaptation this feedback is altered. Rod cone interaction thus tests rod dark current, and cases of abnormal interaction in patients with retinitis pigmentosa occur, which indicate that the transduction mechanism and the membrane dark current may be differentially affected.

There have been several attempts to use psychophysical methods to localise disease conditions to given retinal layers, notably by Enoch and his collaborators,[1] but the methods involved have often been complex and time consuming and have made considerable demands on the patient. However, recently Goldberg *et al.*[2] have described an increase in the cone flicker threshold which occurs as the rods dark adapt. This inhibition of cones by rods has been known for many years,[3] but in the form described the phenomenon is robust, simple to elicit, and is familiar to clinicians. The interaction is developed at a specific retinal site. It therefore promises to be of considerable use in the investigation of retinal disease. Recently properties of the rod-cone interaction have been described.[4-6]

This paper presents additional findings which help to define the nature and the site of the interaction. Equipment for a clinical test is described together with observations which show that the interaction is abnormal in a number of clinical conditions. These provide strong evidence about the site of the interaction, and suggest that study of the phenomenon will increase our understanding of various causes of night blindness.

Material and methods

EQUIPMENT

Most of the initial work was done with the computerised light-emitting diode (LED) perimeter described by Ernst *et al.*[7] This placed 1° green or red spots of light anywhere in the visual field. In the present experiments a site 10° nasally was usually examined. Additional experiments were performed with similar equipment but manually controlled. In one version the filtered LED (light output centred at 660 nm) was attached to one end of a flexible light-pipe, the other end of which was inserted through a hole in a piece of white card, which could be illuminated to produce a dim blue surround. The (460 nm) light which was used to illuminate the surround was provided by a Grass PS22C stroboscope fitted with neutral and colour filters.[8,9] The mean light output was altered by changing the flash rate between 40 and 60 pulses per second (pps) so that, with all the filters in place, the surround was at the rod absolute detection threshold. Under the conditions of the experiments the blue light appeared continuous.

The final equipment utilised both blue and red LEDs. These were driven by a pulse technique. The advantages of this drive, which has been developed from devices previously described in detail,[7,10] are that linear output can be maintained over six decades of intensity: circuits which depend on variable current driving[8] provide linear output over a more limited range of intensities. In addition the pulse driving circuit can provide various stimulus waveforms. Pulses, sine waves, increments, and decrements of light intensity can readily be achieved, and various spatial outputs, for example discs, annuli, chequerboards, etc., are easily realisable. In the present experiments only uniform patches of light were used, and usually flicker was produced by abruptly turning the stimulus light on and off. However, the luminance could easily be made to change in a sinusoidal fashion, and then the modulation depth of the stimulus, defined as $(I_{max}-I_{min})/(I_{max}+I_{min})$, could be varied, so that the modulation thresholds could be determined for every temporal frequency at the same mean level of illumination.

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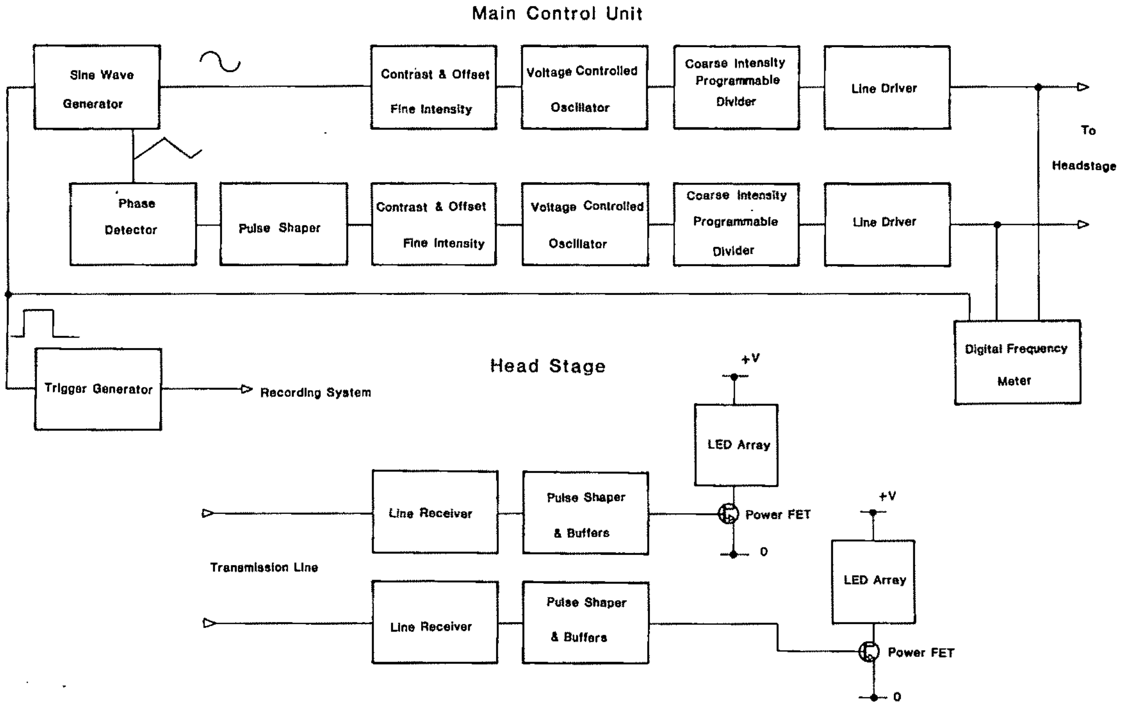


Fig. 1 *Block diagram of the stimulus generator. One channel produces sinewave light outputs from 0·6 to 90 Hz. The modulation depth is continuously variable from better than 99·99% (for all except the weakest stimuli) to 0·1%. The mean light output can be continuously varied over a range of 1000:1, and in addition precise divisions of 2, 5, 10. . . 10^5 are available. The second channel produces pulses of light, from 0·1 to 100 ms, at the same repetition rate as the sinewave. The pulses are phase-locked to the sinewave, and a continuous adjustment of ±176° is possible. For further information see text.*

The block diagram and components are shown in Fig. 1. The waveform generator (Intersil 8038) provides sine, square, and triangle outputs. In the configuration shown the last is fed to a variable trigger point comparator, which thus acts as a phase detector (TLO81CP). The sine wave or pulse outputs are offset and attenuated to provide contrast and mean level controls, using standard operational amplifier techniques. The controls are 10-turn potentionmeters, allowing settings to 1 part in 1000. It would be easy to provide for digital control at this stage if the equipment were to be connected to a computer. The signals alter the frequency of voltage controlled oscillators (VCOs). In the equipment, these are basically similar to the ones described by Faulkner,[7 10] and for an input of 0–2·5 V provide an output from 100 Hz to >5 MHz, with a linearity of >1%. This is a discrete system, but a recently announced single package hybrid (Advanced Modular Concepts, 3800 series) exceeds this specification. The pulses from the VCOs are fed to edge sensitive counters (79LS390), and here divisions of 1,2,5, 10 . . . 10^5 are made for coarse control of light intensity. The pulses (50% duty cycle) are now fed to RS 422 line drivers, so the control equipment can be remote from the light sources. A simple digital meter inserted at this point in the circuit measures the stimulus repetition rate and also the light intensity, since this is directly proportional to the pulse frequency. Standard TTL pulse shapers and buffers are employed to produce 100 ns pulses. These drive power FETs, used as current sinks, which are sufficiently fast to pulse the necessary current and voltage through the LEDs. For all light outputs the current per pulse is constant, thus ensuring linearity. The LEDs are connected in series, and the number used depends on the supply voltage available and the forward voltage drop per LED: this varies with the type used. The peak current pulse used is very much greater than the maximum continuous forward current for the LED, and therefore high light outputs can be achieved, and of course these remain constant for the lifetime of the LED, which is much greater than for incandescent lamps or flash tubes.

In general it is possible to make the drive in such a way that various LED arrays may be plugged into the same unit, allowing for rapid interchange of light sources. The system is easily constructed, since integrated circuits are available for most components, with minimal external circuitry. Component costs are less than for a stroboscope, even for the complex version shown in Fig. 1. Further details are available from the authors. Red, orange, yellow, green, and blue LEDs are now available which will readily provide sufficient light for most physiological purposes, including electroretinography. The only disadvantage is the cost of blue LEDs (US$6 each).

SUBJECTS AND PATIENTS

The authors and associated workers from the clinic acted as subjects. Other results were obtained on volunteers from the department who were au fait with the research and therefore could give informed consent. Other work was done in the course of normal dark adaptometry on patients who were referred for investigation of their eye condition. All observations were made after dilation of the pupil with 1% mydrilate. All subjects and patients had 6/6

Table 1 *Dark adaptation in normal subjects*

No.	*Age*	*Thresholds* at 10'*			*Thresholds at 30'*			*Change from 10–30'*	
		Green	*Red*	*Green-red*	*Green*	*Red*	*Green-red*	*Green*	*Red*
9	32·5±16 (16–70)	−0·32±0·20	0·41±0·51	0·58±0·50	−2·23±0·50	1·12±0·55	−2·12±1·02	−1·91±0·60	0·71±0·30

*Light intensities expressed as log candelas m^{-2}. Mean values and standard deviations are given (equivalent to 3 SEMs). The differences between green and red thresholds, and the change in threshold with time in the dark, are means of the individual values.

vision after spectacle correction, and had no visible fundus changes or complaints apart from the specific problems mentioned in the text.

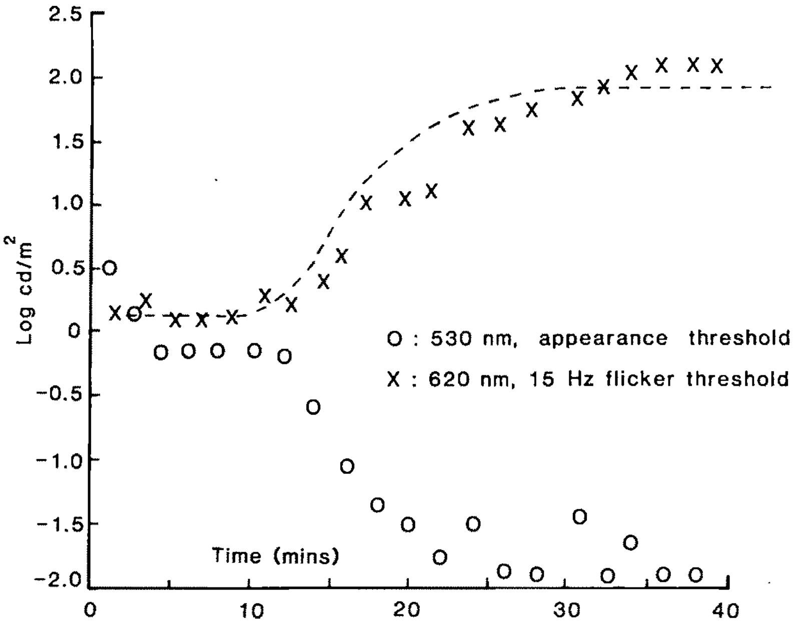
Subjects and patients were light adapted either by using a photographic flash unit connected to a rigid light pipe, or by a tungsten-halide bulb viewed through a Fresnel lens system in maxwellian view. In both cases large areas of the retina (>1 sr) were illuminated by more than 7·5 log td s^{1}, which is sufficient to bleach almost all the rhodopsin.[11]

Psychophysical techniques. In most experiments the method of ascending limits was used, with a computer providing a standard rate of increase of light intensity.[7] In a few cases this was checked by using a forced choice staircase method, with ascending and descending intensities, and the threshold was then taken as the point where the probability of correct positive and negative responses was equal. In static conditions the results obtained by the two methods were similar, but the forced choice method was laborious and not suited to measurement of changing thresholds.

Results

Dark adaptation curves measured with red light flashes showed a rapid increase of cone sensitivity, which was essentially complete after three minutes.[3 4 7 11] After about 20 minutes rod dark adaptation might have progressed so far that even far red light was perceived best by rods, and a further slight decrease in threshold might occur.[7] Whether this is seen depends upon whether the red test flash sub-

Fig. 2 *Dark adaptation curves in a subject with an exaggerated rod-cone interaction. The test stimuli were placed 10° nasally, subtended 1° at the eye, and were produced by filtered green and red LEDs. The preadaptation was by an intense flash which bleached most of the retinal rhodopsin. Each point is the average of two determinations of visual threshold. A computer caused a steady increase in the intensity of the test light, and recorded the intensity when the patient responded by pressing a button. Each run began at a randomly selected subthreshold intensity. The computer continued to test the subject until the standard deviation of the threshold fell below 0·2 LU. Green threshold and red flicker threshold determinations alternated. Note that the red flicker threshold begins to rise at about the time of the rod break in the green threshold curve. The dashed line is the reciprocal of the rod threshold. The exact threshold levels and the magnitude of the change in rod threshold vary across the retina, but it is evident that there is a close correspondence between the kinetics of rod dark adaptation and the rise in cone flicker threshold to red light.*



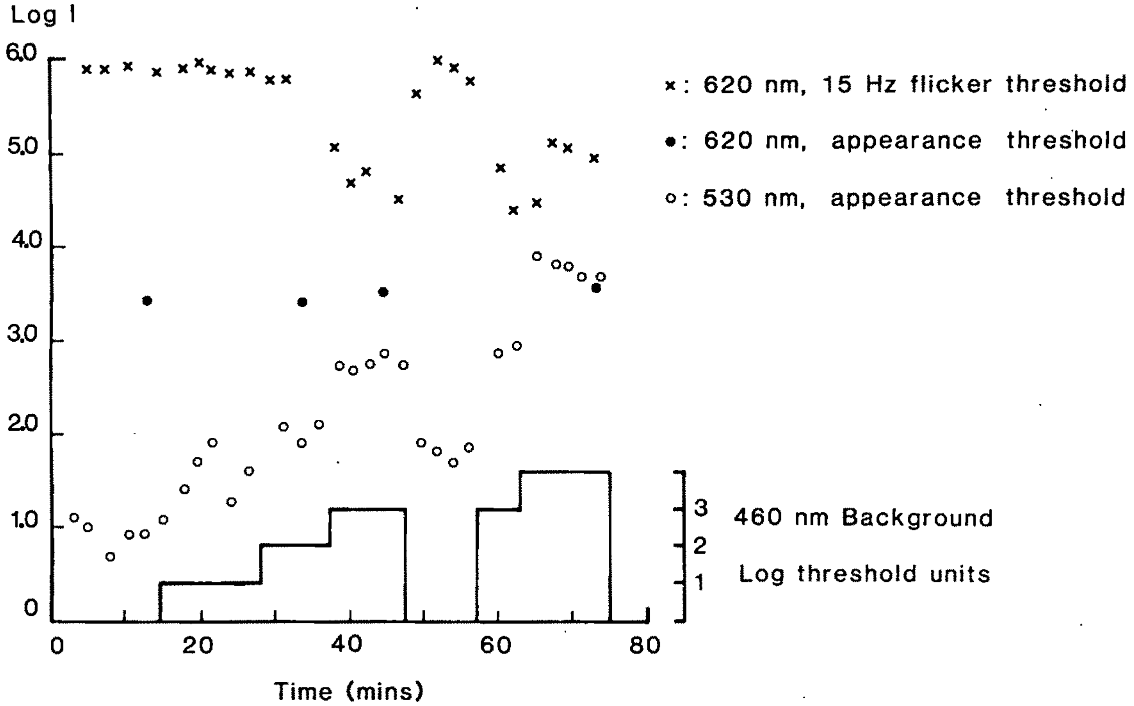


Fig. 3 *Increment thresholds in a second subject with an exaggerated rod-cone interaction. The background was a 10° disc illuminated by 460 nm light (see 'Material and methods'). The subject dark adapted, and then visual threshold was determined for the background. The right hand ordinate gives the intensity in multiples of this threshold. Note that the threshold for detecting the red light (at 15 Hz, the sensation evoked is of a continuous constant luminosity) is unchanged by the rod background until, with four log units of filter removed, the threshold rises slightly. In contrast, the flicker threshold for red light drops when the background is increased. Other conditions similar to those for Fig. 2.*

tends a large area, and is placed in a region of high rod density. However, if the stimulus is a 15 Hz square wave flicker, and the subject is asked to report not when he sees the light but when he sees it *flicker*, a very different result occurs. From about the 10th to the 25th min after the beginning of dark adaptation the flicker threshold rises, by over half a log unit.[2] Table 1 gives the range for our 'normal' subjects. The slow time course of this change and the fact that it began almost at the moment of the rod-cone break suggests very strongly that the rod dark adaptation was causing the loss of sensitivity of cones.

In some persons the rise is much greater. We have found three of these, and all complained of difficulty with night vision, specifically in driving at night. Fig. 2 shows the result obtained in a patient aged 30, who had been seen for 10 years. No abnormality had ever been detected, but the patient, who is medically qualified, was positive he and other members of his family were visually impaired in dim light conditions. Since cone and rod thresholds were normal by a Goldmann-Weekers adaptometer, a possible psychogenic disturbance had been discussed. However, the threshold for detecting cone flicker rises by about 2·5 log units as the rods dark adapt, and because the effect is so large its kinetics are easy to study. The dashed curve in Fig. 2 gives the reciprocal of rod threshold, and it can be seen there is good agreement between it and the cone threshold data. Similar results have been found on other subjects (Fig. 6). One of these, a laboratory technician aged 39, volunteered that she had difficulty in driving at night and in seeing kerb markings. Another of our colleagues, hearing of these results, suggested he should be tested, and he also had a large rise of flicker threshold. However, another subject who claimed he had the same disability had a threshold rise of only 0·6 log unit.

The appearance of the cone inhibition can be reversed by using a background which stimulates only rods. Fig. 3 shows this, again on a subject with an exaggerated effect. It can be seen that 3 log units of background were required before the cone flicker threshold abruptly fell. At visual threshold only a small fraction of the rods—perhaps one in a hundred —absorbed a quantum of light per second. Thus the

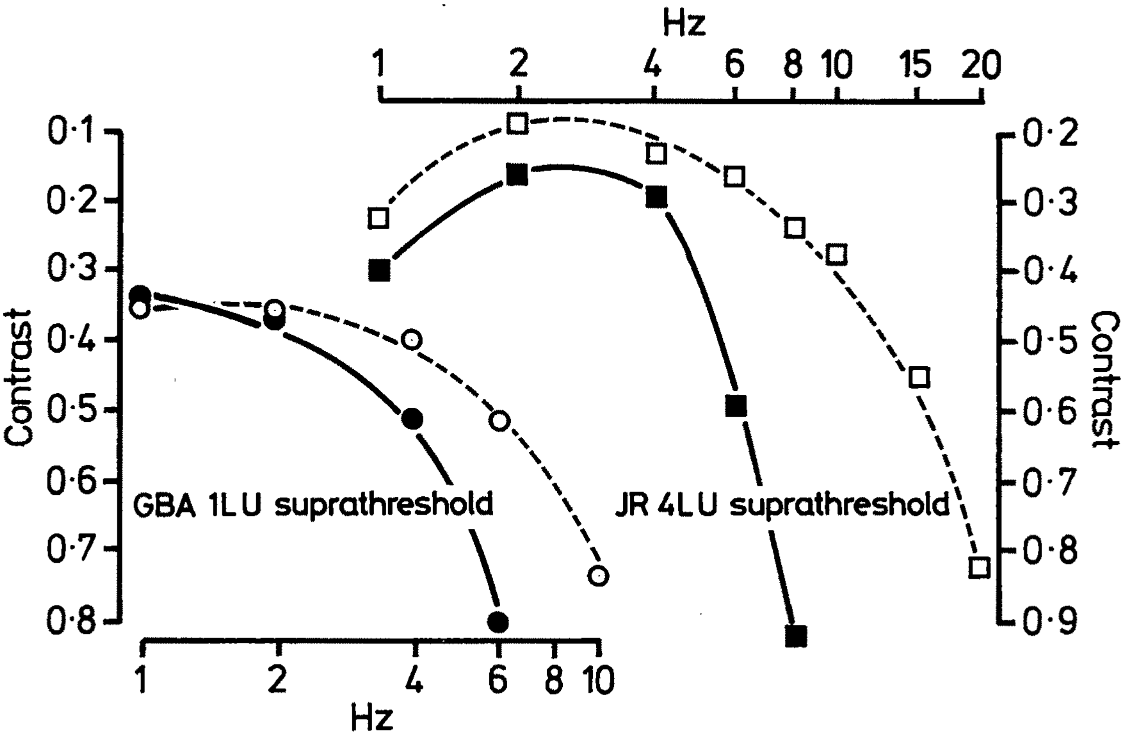


Fig. 4 *Modulation threshold curves for one of the authors (left panel) and the subject whose results are shown in Fig. 3 (right panel). In the former case the red test light was 1 log unit above the threshold for detection in darkness. For the latter the intensity was 4 log units. In both cases the backgrounds were 3 log units above the threshold of the rods and thus just below threshold for red cones. Closed symbols without, and open symbols with, a background. Note that the background does not affect modulation sensitivity for the 1 Hz sinewave red test, but reduces it for higher temporal frequencies.*

illumination which causes the fall in cone flicker threshold is one where all the rods are continuously stimulated, but the rod dark current is reduced but not abolished.[12 13] The rapid increase of the cone threshold when the rod background is turned off is what would be expected under such circumstances. Such a background, while effective in stimulating rods, is still subthreshold for the red cones. Note that 4 log units suprathreshold light was required to increase the cone flash threshold.

The inhibition of the cone signal occured only at higher temporal frequencies. Fig. 4 presents the modulation curves for two subjects, and it can be seen that, while for low frequencies (1 Hz) the threshold modulation was unaffected by the background, for higher frequencies the effect became progressively greater: Dark adapted rods seemed to interpose a low-pass filter into the cone pathway.

The effect of backgrounds is not critically dependent on the light intensity used in the red test. Fig. 5 shows results obtained when it is set at 1, 3, and 4·3 log units above the 1 Hz detection threshold. For all these values the effect of the background was to decrease the depth of modulation required to see the flicker. The ability to detect the flicker was much greater for the stimulus which was 3 LU above threshold, but the further increase caused little change either in the dark adapted condition or in the presence of a background. Thus the effect of the background cannot (within these limits) be mimicked by increasing the intensity of the test light. These observations are incompatible with the idea that the effect is somehow spurious and produced by subliminal stimulation of the cones by the rod stimulus.

Another observation which shows that a novel form of interaction is occuring is that the rise of flicker threshold was seen only if the red test field was relatively small: the rise of approximately 2 LU shown in Fig. 6 was totally absent if a 50° field was used as a test target (Fig. 6).

ROD-CONE INTERACTION IN PATIENTS WITH ABSENCE OF ROD B WAVES

The site of the interaction between the rod and cone pathway can be investigated by utilising clinical pathology. In nyctalopia there is a failure of synaptic

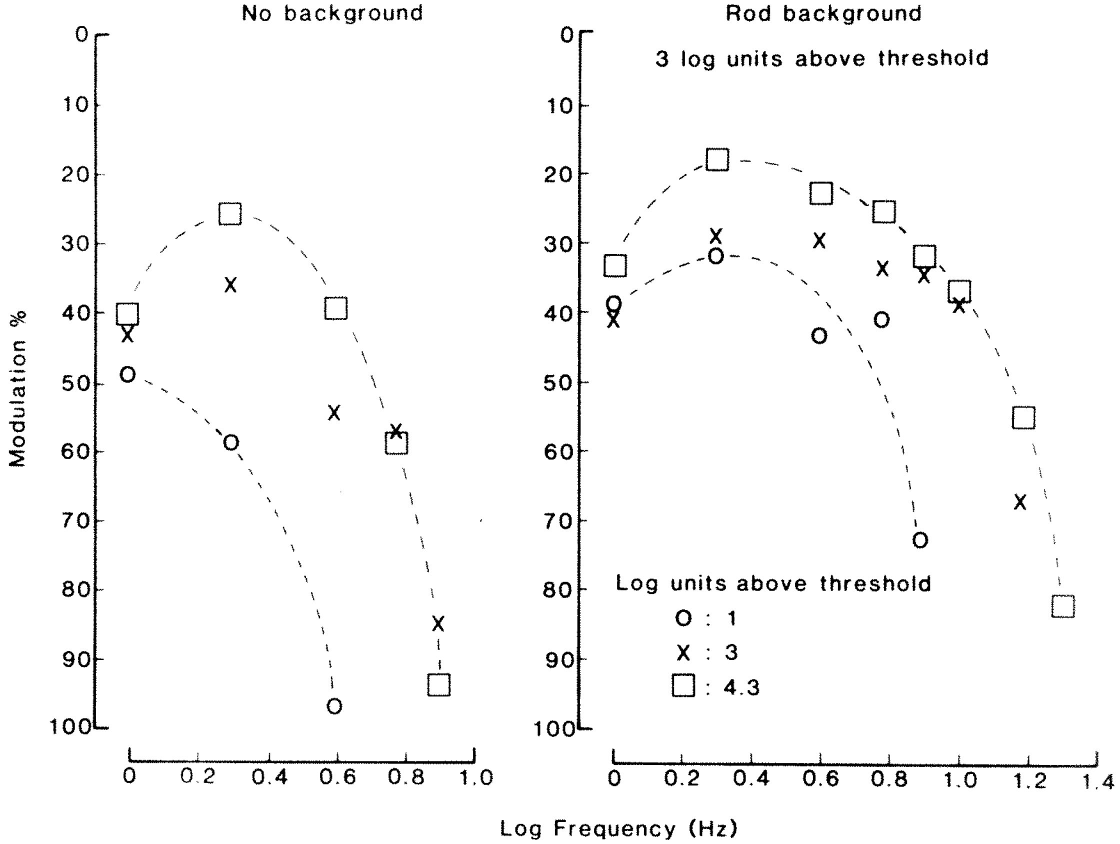


Fig. 5 *Modulation thresholds as a function of test light intensity, without a background (left) and with a background (right). Note that for test lights 3 and 4·3 log units above the detection threshold the high frequency modulation thresholds are not greatly different, but there are large effects of the 460 nm background, which is 3 log units above the rod threshold.*

transmission by rods, though rhodopsin is present, and there is electroretinographic evidence that only the rod receptor potential is developed.[11 14 15] Consequently, if the rod-cone interaction occurs at a site which preceeds the development of the b wave, it should be developed in nyctalopes. Fig. 1 in Arden and Hogg's paper[4] shows that in one patient this is not the case. Various forms of nyctalopia have been described[11 14–17] and our patients fall into two groups—those with and those without elevation of the cone flicker threshold. Table 2 shows the thresholds after 5 minutes and 20–30 minutes of dark adaptation in this group. All the patients had classical electroretinograms, consisting of rod PIII and some cone b wave. The mean rise in the flicker threshold is −0·025 LU.

The appearance of an isolated rod PIII also occurs in some cases of X-linked retinoschisis.[15 18] In young patients vision is well preserved, and schisis at the posterior pole is patchy, so large cysts such have been reported in the literature are not formed. The fundus photograph of the eye is shown in Fig. 7. Dark adaptation thresholds are normal or moderately elevated. In cases such as these (see the caption to fig. 8 for further details) the cone flicker threshold does not rise during rod dark adaptation (Fig. 8). However, in one family, the results are variable, and this is not surprising, for so too is the degree of schisis. The cases we have seen differ from the nyctalopes in one respect, that rods continue to function though there may be an elevation of the dark adapted threshold.

ROD-CONE INTERACTION IN RETINITIS PIGMENTOSA

In some cases where there is no detectable rod function (type 1, see Arden *et al.*,[9] Massof and Finkelstein[19]) rod-cone interaction has not been seen, though cone threshold was not significantly elevated. In one patient with type II disease and well preserved rod function the effect was present, though reduced (Fig. 9). In another patient with type II disease there

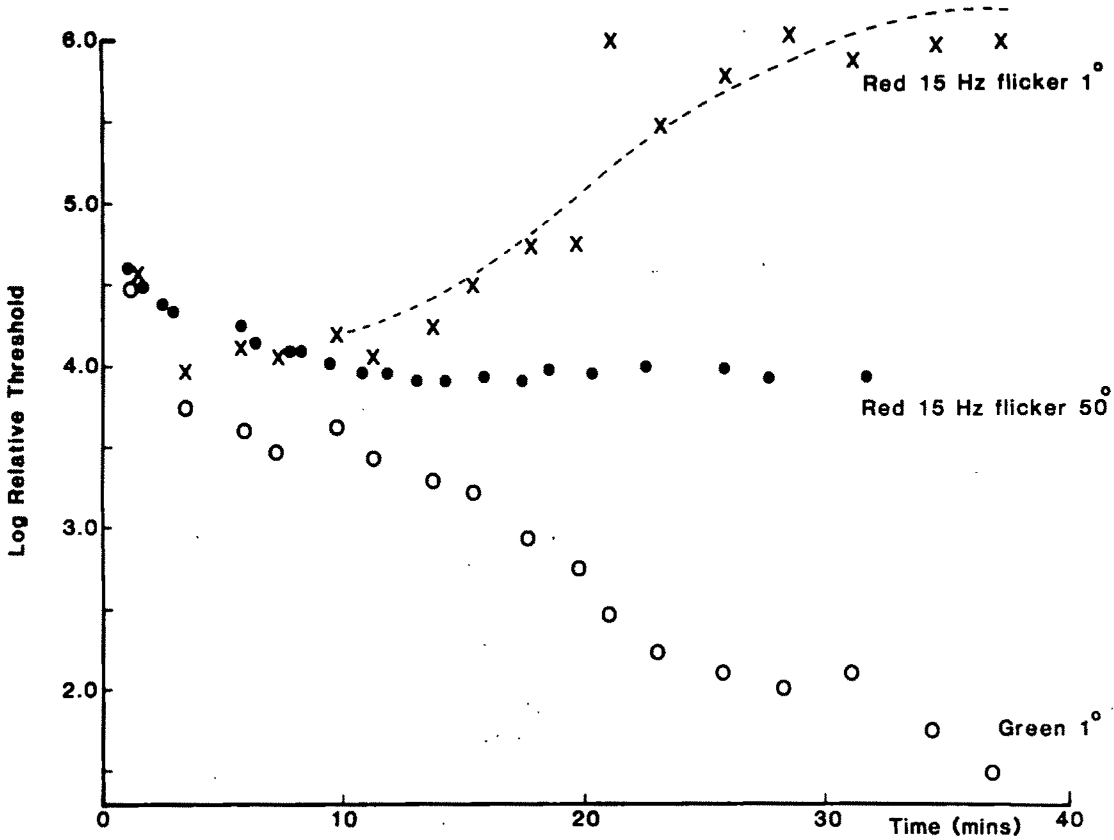


Fig. 6 *Dark adaptation curves from a subject with an exaggerated rod cone interaction. Conditions for the 1° green and red fields are similar to those in Fig. 2. Note the cone data also agree with the reciprocal of the rod threshold (dashed curve). However, when the red flickering light subtended c. 50°, the interaction is absent. The test stimulus was made by backprojecting red LEDs on to an opal screen, which also carried another small LED for fixation. The test spot subtended 6 cm and was placed 6 cm from the eye.*

was slowed dark adaptation,[20] and a normal sized increase in the cone flicker threshold occurred at a time when the patient's rods were very insensitive. No further change occurred as they gradually recovered (Fig. 10) and threshold for green light fell to nearly normal limits.

Discussion

The rod-cone interaction described[2] is a very robust phenomenon, and can easily be measured by a simple modification of most dark adaptometers. It is consequently a practical clinical test. Patients easily comprehend the idea of distinguishing between the appearance of a light and the development of a sensation of flicker. The threshold for detection of a red light flickering at 15 Hz is little different from that of a non-flickering red light, and during the early part of the cone plateau the thresholds for detection and recognition of flicker in most patients are nearly the same. Consequently, even if the adaptometer is modified so that the red test spot always flickers, there is no loss in terms of the information available, and there are the gains described above, in terms of diagnosis of complaints of loss of night vision.

One of the new findings made in the course of the investigation is that there are persons in whom the rod cone interaction is exaggerated, and that these persons either present with the complaint or volunteer the information that they have difficulty in seeing at night. Although in many cases where no retinal cause can be found subjective nyctalopia may be due to aging processes, which reduce retinal illumination or cause glare, or to night myopia, there remains a core of patients in whom, as demonstrated above, dark adapted rods seem to cause gross inhibition of the sensation caused by small, rapidly changing objects. The task which one would predict would be

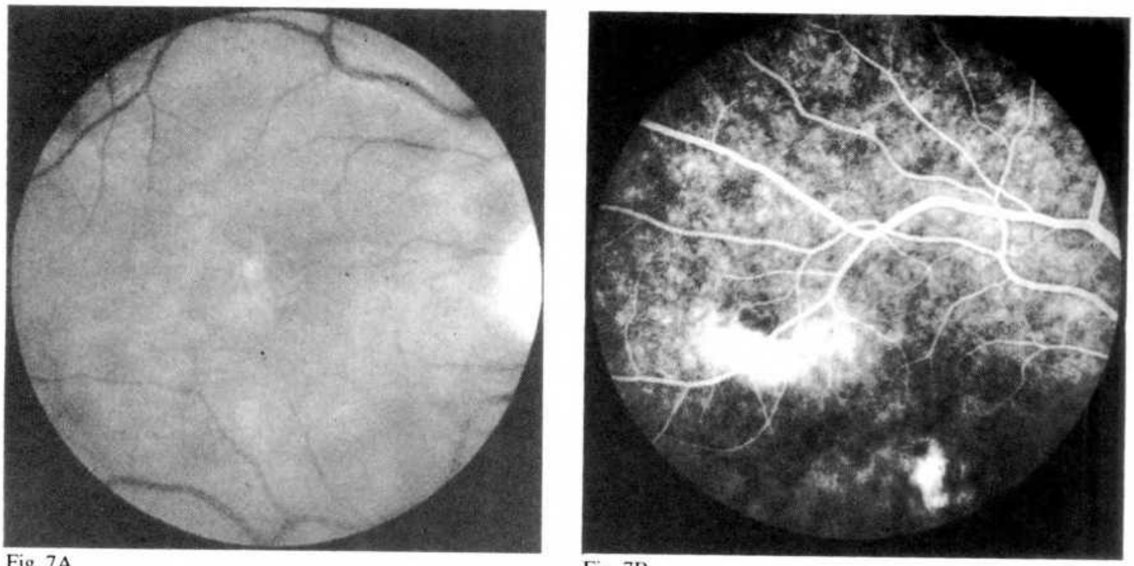


Fig. 7A Fig. 7B

Fig. 7 A: *Fundus photograph of patient with X-linked retinoschisis, case 13011, whose ERGs and dark adaptation curves are shown in Fig. 8.* B: *Early phase fluorescein angiogram of peripheral retina in same subject.*

difficult for such persons is night driving, and this is the presenting complaint. It is therefore plausible that abnormally active rod-cone interaction can be a hitherto unsuspected cause for referral to an ophthalmologist. In the absence of other signs and symptoms, and before the demonstration that all people such as those whose results are shown in Fig. 2–6 have actual visual disability, it is premature to suggest that the test has uncovered a new disease. However, it is possible that in one of our patients, the condition is familial.

MECHANISM OF ROD-CONE INTERACTION

Depending on the cause of the interaction, the test can shed light on the pathophysiology of disease, and for this reason our first investigations have been directed to this end. In the mammalian retina there are numerous gap junctions between rods and

Table 2

Patient No.	*Age*	*VA*	*EOG*	*ERG*	*Thresholds**				*Rod-cone interaction*†
					At cone plateau		*Final value*		
					Red	*Green*	*Red*	*Green*	
Summary of data on patients with X-linked retinoschisis									
13011	22	6/6	117	−ve	0·35	0·35	0·1	−1·70	−0.25
11806	46	6/60	178	subnormal	0·00	—	0·5	—	0·5
13565	59	6/60	—	−ve	0·45	0·5	0·3	−1·43	−0·15
13331	48	6/36	—	−ve	0·15	−0·25	0·05	−1·70	−0·10
13493	10	6/18	200	reduced b waves	0·10	−0·65	0·80	−2·05	0·70
13494	6	6/6	240	reduced b waves	−0·25	−0·25	−0·40	−2·02	−0·15
Summary of data on patients with stationary night blindness‡									
13500	36	6/6	—	−ve	0·45	0·80	0·35	0·60	−0·10
13425	48	6/18	—	−ve	2·30	0·50	2·30	0·50	0
13490	34	6/6	—	−ve	0·30	0·35	0·30	0·30	0
14085	22	6/12	—	−ve	2·10	0·08	2·10	−0·40	0·0

*Threshold values in log cd.m^{-2}.

†Normal interaction is given a +ve sign.

‡All patients had full fields with no scotomata, no ophthalmoscopic changes in the fundus, a history of nyctalopia for many years, and no evidence on repeated visits of any progressive disorder.

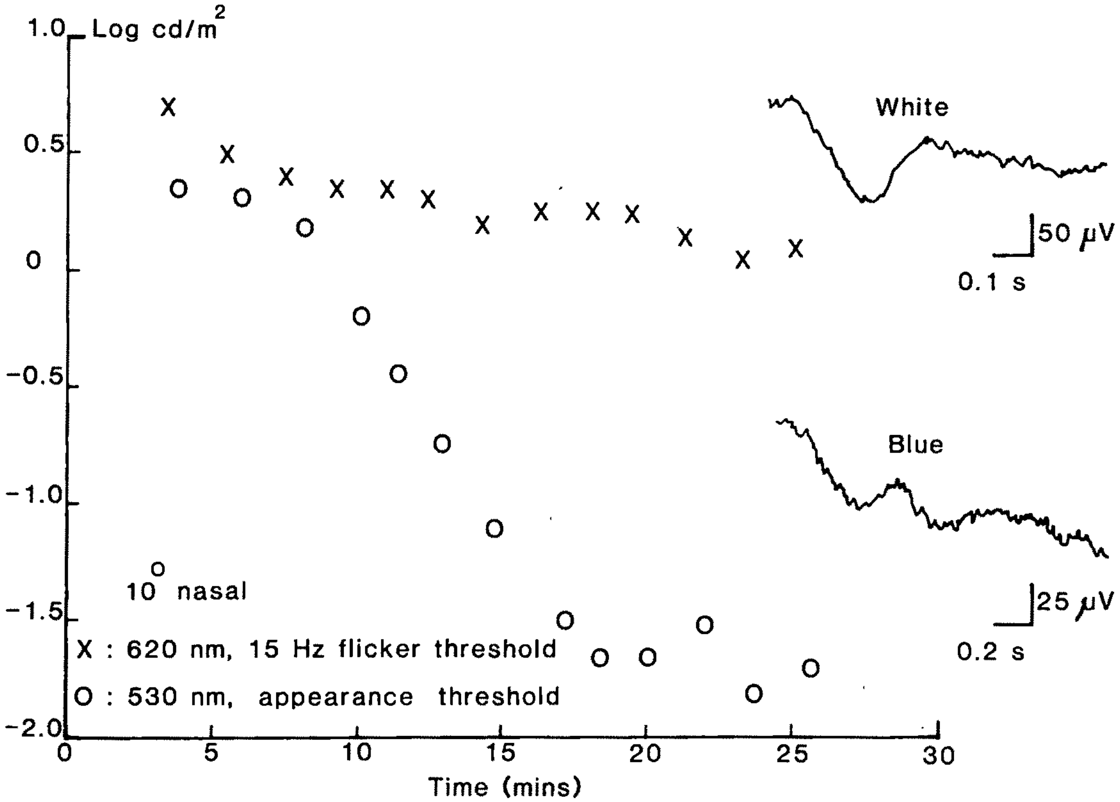


Fig. 8 *Dark adaptation curves and ERGs of a patient with X-linked retinoschisis, aged 22. He was first seen aged 8, with reduced visual acuity, when macular changes were noted. He was seen again in 1983, with VA 6/36 R and L, with a small right vitreous haemorrhage inferonasally. Macular and perimacular changes were seen, and leakage was shown round the disc and in the periphery on fluorescein angiography. The retina was flat, but 'looked like Cellophane.' The ERG was negative, and the light rise in the electrooculogram (the EOG) was 200% in each eye. Twelve months later the vitreous haemorrhage had resolved and visual acuity was unchanged. The areas of schisis were discrete and limited to the posterior pole. The white and strong blue ERG stimuli produced the responses shown, with large* a *waves, and very subnormal* b *waves, but the EOG of the R eye had fallen to 116% The green light rod dark adaptation curves are nearly normal. The flicker thresholds for red light remain constant as the rods dark adapt. The conditions of the test were the same as those for Figs. 2 and 6.*

cones,[21] so that presynaptic interaction is possible. The results with nyctalopia provide good evidence that the interaction is postsynaptic. The absence of the interaction in patients with retinoschisis, who are not night blind, implies that the bipolar cell—ganglion cell pathway itself cannot mediate the interaction. The finding that the interaction interposes a low pass filter in the cone pathway, but that this effect is absent or reduced when the cone test stimulus has a very large subtense, suggests strongly that the rod interaction occurs via a lateral interaction with a large spatial summation pool, and the earliest site for this to happen is the horizontal cell, which has such characteristics.[22-24] In mammals horizontal cells are known to form synapses with both rods and cones,[21 25-28] and the axon terminations receive predominantly rod inputs. All S potentials recorded contain rod and cone components, but the potentials are additive. The inhibition of cones by rods is not directly explicable from such observations. However, an inhibitory action which is well known involves the feedback to cones[12 22 29] from horizontal cells. This has been demonstrated only in turtles and amphibia, where intracellular recordings from photoreceptors is possible, but the synaptic appearances in the primate outer plexiform layers suggest a similar organisation. The effect of the feedback is to reduce the cone receptor potential waveform[29] after a delay, so that the flash evoked response reaches its peak and then suddenly decreases. As expected, this feedback improves the high frequency response of the cone system.[30 31]

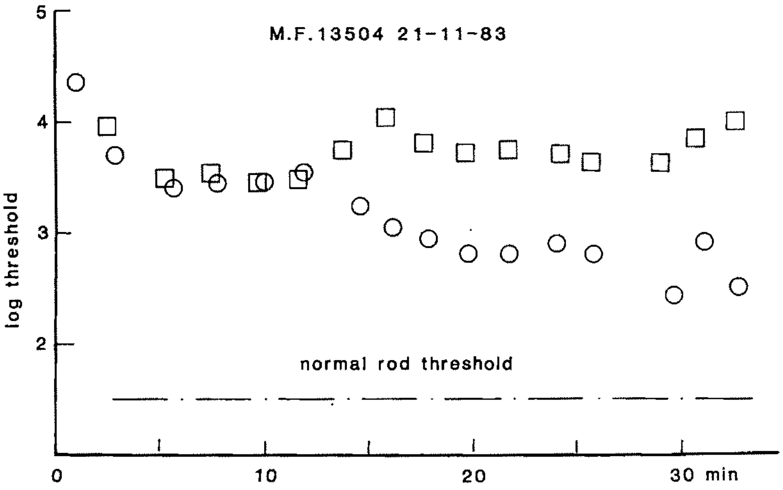


Fig. 9 *Rod cone interaction in a patient with retinitis pigmentosa, aged 70. The patient's condition was discovered when she went to an optician for reading glasses. The fundi showed extensive pigmentation in the midperipheral zone, much of it in bone corpuscle clumps, but the posterior pole was relatively free of pigmentation. Retinal vessels were attenuated, and the disc normal. Goldmann fields showed an irregular constriction most severe in the upper visual fields. The ERGs were reduced to about half size, but there was no change of sensitivity (see Arden et al.[9]) and dark adapted rod thresholds (circles) were slightly elevated at the retinal locus tested. The elevation of cone flicker threshold is c. 0·3 LU, which is considerably below the normal mean value.*

The simplest explanation of the findings described under 'Results' is that late in dark adaptation the cone feedback system becomes relatively inefficient, so that the high frequency responsiveness of the photopic system is decreased. Horizontal cells, like photoreceptors, are depolarised in darkness and are supposed under these conditions to liberate continuously an inhibitory transmitter. Hence when a stimulus hyperpolarises the cones, and the horizontal cell membrane hyperpolarises in turn, there is a small proportional decrease in the concentration of the inhibitory feedback transmitter. When rods hyperpolarise, the horizontal cell follows suit, the concentration of the inhibitory feedback transmitter declines, and the fractional change in transmitter caused by the same cone signal increases. In addition it is possible that the relationship between horizontal cell membrane potential change and the rate of liberation of feedback transmitter is optimised for the light adapted state. A given cone signal would then cause a maximal change in feedback transmitter

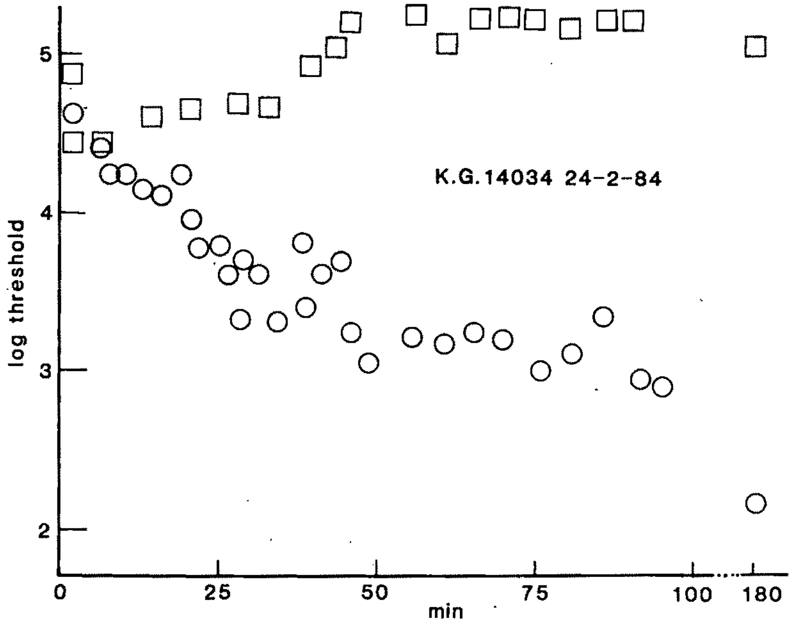


Fig. 10 *Rod cone interaction in a patient with retinitis pigmentosa. This 24-year-old woman came from a family with autosomal dominant disease. When she was first seen the ERGs, fields, and rod thresholds were only slightly affected. In the few months before the test her condition had deteriorated, and the slow dark-adaptation curve shown was obtained. Note that after three hours the rod threshold (circles) was nearly normal. Cone flicker threshold (squares) rises after an unusual delay, but is quite pronounced. However, at the time of the rise the rods are extremely insensitive.*

output when the horizontal cell was partially hyperpolarised.

When the cone stimulus covers a large retinal area, it produces larger horizontal cell responses than when it subtends a small visual angle, and therefore the feedback may still be effective in the dark adapted eye. In the first few minutes after intense light adaptation, the rat rod receptor potential is maintained[13] in the hyperpolarised state, but later the dark current returns once more along a time course that (in axolotl rods[32]) approximates to, but is not identical with, that of the recovery of sensitivity to light, thus accounting for the attenuation of the cone flicker signal during rod dark adaptation.

Following intense bleaching there is a large after-hyperpolarisation in cat horizontal cells, which lasts for many seconds, but the time course of recovery may be faster than the rate of rhodopsin regeneration.[25,26,33] In turtle cones[12,22] the horizontal cell feedback is best seen and operates between different classes of cones, but it has been reported[5] that in man the interaction occurs only between rods and red cones; little is known about the feedback in mammalian or primate receptors. An alternative hypothesis is that the rods control the horizontal cell membrane potential indirectly, through an interplexiform cell feedback.[34]

CLINICAL IMPLICATIONS

The appearance and magnitude of the rod-cone interaction described above would, on our hypothesis, depend upon the time and extent of the rod dark current. In those persons with exaggerated effects, perhaps the effectiveness of the rod transmitter in depolarising the horizontal cells is greater than normal. In our cases of X-linked schisis the reduction of the inhibition of cones by rods implies that the horizontal cell feedback must be reduced, but the relationship to pathological changes is not certain. In elderly persons cystic degeneration affects the outer retina, so that in the end a few bipolar cells mark the limits of the cysts, and it is entirely plausible that the lateral connections of horizontal cells are disrupted. In X-linked schisis the split is supposed to be in the nerve fibre layer or the inner plexiform layer.[15,35–37] However, the evidence is not conclusive, and the patients from whom the histological results were derived were not investigated by ERG, so it is not known if they were of the type we have seen. The lesions were much more severe than in our patients.

If the hypothesis advanced above is correct, this form of rod-cone interaction measures the integrity of the outer plexiform layer and also provides an index of the function of the rods which is independent of whether visual transduction occurs normally. Thus in retinitis pigmentosa we can show that in some cases, although there is a moderate reduction in sensitivity, the interaction is present. This would be consistent with the idea that there was a reduced rod dark current input to horizontal cells. In one case change in cone sensitivity is dissociated (Fig. 8) from the change in rod sensitivity, and hence on this argument dissociated from the rod membrane current. Therefore it is likely that in this patient the plasma membrane processes may be normal, while the intracellular mechanisms which control rod sensitivity are affected by the condition. Detailed analysis of selected patients is under way to determine whether reduction in membrane current and reduction of rhodopsin concentration run in parallel. This might answer the question whether rods in retinitis pigmentosa are shortened or disorganised.

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References

1 Enoch JM. Quantitative layer-by-layer perimetry. *Invest Ophthalmol Visual Sci* 1978; **17:** 208–57.

2 Goldberg SH, Frumkes TE, Nygaard RW. Inhibitory influence of unstimulated rods in the human retina: evidence provided by examining cone flicker. *Science* 1983; **221:** 180–1.

3 Lythgoe RJ, Tansley K. Reports of the Committee upon the Physiology of Vision. Medical Research Council Special Report Series 1929; **134:** 72.

4 Arden GB, Hogg C. Absence of rod cone interaction in nyctalopia and retinoschisis. *J Physiol (Lond)* 1984; **353:** 19P.

5 Colletta NJ, Adams AJ. Rod-cone interaction in flicker detection. *Invest Ophthalmol Visual Sci* 1983; **24** (ARVO suppl): 187.

6 Alexander KR, Fishman GA. Rod-cone interaction in flicker perimetry. *Br J Ophthalmol* 1984; **68:** 303–9.

7 Ernst W, Faulkner DJ, Hogg CR, Powell DJ, Arden GB, Vaegan. An automated static perimeter/adaptometer using light emitting diodes. *Br J Ophthalmol* 1983; **67:** 431–42.

8 Nygaard RW, Frumkes TE. LEDs: convenient inexpensive sources for visual experimentation. *Vision Res* 1982; **22:** 435–40.

9 Arden GB, Carter RM, Hogg CR, *et al.* Rod and cone activity in patients with dominantly inherited retinitis pigmentosa: comparisons between psychophysical and electroretinographic measurements. *Br J Ophthalmol* 1983; **67:** 405–13.

10 Faulkner DJ. A new television visual stimulator for contrast sensitivity and evoked response testing. *J Physiol (Lond)* 1978; **275:** 7P.

11 Ripps H. Nightblindness revisited: from man to molecules. *Invest Ophthalmol Visual Sci* 1982; **23:** 588–609.

12 Baylor DA, Hodgkin AL. Detection and resolution of visual stimuli by turtle photoreceptors. *J Physiol (Lond)* 1973; **234:** 163–98.

13 Hagins WA, Penn RD. Kinetics of the photocurrent of retinal rods. *Biophys J* 1972; **12:** 1073–94.

14 Carr RE, Siegel IM. Ocular Electrodiagnosis. Baltimore: Williams and Wilkins, 1982.

15 Krill AE. *Hereditary retinal and choroidal diseases*. Hagerstown: Harper and Row, 1977: **2.**

16 Duke-Elder S. *A system of ophthalmology*. London: Chapman and Hall, 1964: 3 (2).

17 Kelsey JH, Arden GB. Acquired unilateral loss of dark adaptation. *Br J Ophthalmol* 1971; **55:** 38–43.

18 Thaler A, Heilig R, Slozak H. Elektroretinogram und Elektrooculogram bei juvenile Retinoschisis. *Klin Monatsbl Augenheilkd* 1973; **163:** 699–703.

19 Massof RW, Finklestein D. Rod sensitivity relative to cone sensitivity in retinitis pigmentosa. *Invest Ophthalmol Vis Sci* 1979; **18:** 263–72.

20 Alexander KR, Fishman GA. Prolonged dark adaptation in patients with retinitis pigmentosa. *Br J Ophthalmol* in press.

21 Nelson E, Kolb H, Famiglietti EV Jr, Gouras P. Neural responses in the rod and cone systems of the cat retina: intracellular records and procion stains. *Invest Ophthalmol Visual Sci* 1976; **15:** 946–53.

22 Baylor DA, Fuortes MGF, O'Bryan PM. Receptive fields of cones in the retina of the turtle. *J Physiol (Lond)* 1971; **214:** 265–94.

23 Simon EJ. Two types of luminosity horizontal cells in the retina of the turtle. *J Physiol (Lond)* 1973; **230:** 191–211.

24 Lamb TD. Spatial properties of horizontal cell responses in the turtle retina. *J Physiol (Lond)* 1976; **263:** 239–55.

25 Steinberg RH. Rod and cone contributions to s-potentials from the cat retina. *Vision Res* 1969; **9:** 1319–29.

26 Steinberg RH. Rod-cone interaction in s-potentials from the cat retina. *Vision Res* 1969; **9:** 1331–44.

27 Niemeyer G, Gouras P. Rod and cone signals in s-potentials of the isolated perfused cat eye. *Vision Res* 1973; **13:** 1603–12.

28 Nelson R. Cat cones have rod input: a comparison of the response properties of cones and horizontal cell bodies in the retina of the cat. *J Comp Neurol* 1977; **172:** 109–35.

29 Fuortes MGF, Schwartz EA, Simon EJ. Colour-dependence of cone responses in the turtle retina. *J Physiol (Lond)* 1973; **234:** 199–216.

30 Naka K, Sakuranaga M, Chappell RL. Wiener analysis of turtle horizontal cells. *Biomed Res* 1982; **3** (suppl): 131–5.

31 Lassater EM, Lam DMK. The identification and some functions of GABAergic neurons in the distal catfish retina. *Vision Res* 1984; **24:** 497–506.

32 Ernst W, Kemp CM, Lake N. Studies on the effects of bleaching amphibian rod pigments. IV. Photoresponses recorded intracellularly from axolotl red rods following bleaching flashes. *Exp Eye Res* 1978; **27:** 117–27.

33 Steinberg RH. The rod after effect in s-potentials from the cat retina. *Vision Res* 1969; **9:** 1345–55.

34 Dowling JE, Ehinger B, Hedden WL. The interplexiform cell: a new type of retinal neuron. *Invest Ophthalmol Visual Sci* 1976; **15:** 916–26.

35 Zimmerman LE, Spencer WH. The pathologic anatomy of retinoschisis with a report on two cases diagnosed as malignant melanoma. *Arch Ophthalmol* 1960; **63:** 10–9.

36 Yanoff M, Rahn EH, Zimmerman LE. Histopathology of juvenile retinoschisis. *Arch Ophthalmol* 1969; **79:** 49–53.

37 Manschot WA. Pathology of hereditary juvenile retinoschisis. *Arch Ophthalmol* 1972; **88:** 131–8.

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Retinal microangiopathy and pigment epithelial lesions in subjects with normal, borderline, and decreased oral glucose tolerance

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SUMMARY Retinal fluorescein angiography was performed in 150 subjects: 64 with normal fasting blood glucose and normal oral glucose tolerance test (OGTT), 49 with borderline, and 37 with decreased OGTT. Microaneurysms were noted in only two subjects, both with decreased OGTT. Minute changes in the retinal pigment epithelium (RPE) were seen in 23% of the 64 normal persons, in 35% of those with borderline, and 49% of those with decreased OGTT ($p<0·05$). The impact of glucose intolerance was more pronounced in subjects under the age of 50 years, RPE changes being rare (7%) in those with normal OGTT but occurring in 32% of those with borderline or decreased OGTT ($p<0·01$). The corresponding figures among subjects aged 50 or more were 55% and 57%, respectively. We conclude that at least half of the subjects above 50 years show RPE alterations, and that minimal changes in glucose metabolism may precipitate the development of such changes at an earlier age.

The presence of microaneurysms and more advanced signs of diabetic retinopathy at the time of diagnosis of manifest diabetes mellitus has long been recognised and has been reported to occur in 4–15% of such patients.[1] Changes compatible with diabetic retinopathy have also been observed in some subjects with decreased oral glucose tolerance (OGTT) only,[2] as well as in a few with normal OGTT but with renal lesions of the diabetic type.[3]

It has recently been reported that minute changes in the retinal pigment epithelium (RPE), visible both on fluorescein angiograms and colour photographs, occur in about 30% of normal subjects.[4] Since RPE has a high metabolic activity and great phagocytic capacity, the question arises whether alterations of RPE precede apparent diabetic vascular changes in the retina. We have therefore investigated the prevalence of RPE changes in younger (<50 years of age) and older (≥50 years) subjects with and without minor impairment of glucose metabolism.

Material and methods

SUBJECTS

The study included 150 subjects (54 females, 96 males), 64 of whom had normal fasting blood glucose and normal OGTT (Table 1). Forty-nine of the subjects had borderline and 37 decreased OGTT. Their age ranged from 23 to 72 years. Those with borderline or decreased OGTT were matched with normal controls for age, sex, and body weight.

All subjects participating in the study were apparently healthy. On the basis of detailed case histories, physical examinations, and a series of laboratory tests, the following diseases could be excluded: anaemia, heart failure, hypertension, liver and kidney disease, malabsorption, and endocrine disorders. In addition in all subjects the insulin response to oral glucose and glucose infusion was measured, and estimates were obtained for insulin secretory capacity and insulin sensitivity.[5]

METHODS

Oral glucose tolerance test (OGTT). Glucose was given orally in 300 ml of water in a dose of 1·75 g per kg body weight, and venous blood samples were

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collected from an indwelling catheter before and at 15, 30, 45, 60, 90, and 120 min. OGTT was assessed according to the criteria in Table 1, which were adopted from those of Reaven *et al.*[6] *Glucose* in whole blood was measured with glucose oxidase.

The *ophthalmological examination* included measurements of visual acuity and intraocular pressure, as well as slit-lamp biomicroscopy and ophthalmoscopy.

Fluorescein angiography of the fundi was performed with a Zeiss fundus camera (Oberkocken, West Germany) equipped for angiography (excitation filter: Schott BG 12; barrier filter: Schott GG 14). 5 ml of a 10% solution of sodium fluorescein was injected into an antecubital vein. A standard 30% view of the posterior pole of the fundus (centring the macular area) was photographed in both eyes at 1–2 s intervals during the first 30 s and later at about 15 s intervals for 3 min. Mydriasis was induced by topical tropicamide (Mydriacyl) and cyclopentolate (Cyclogyl). Fundus photographs in colour were taken from both eyes. The colour slides were projected on a screen and examined under magnification (X 8). The black and white prints of the angiograms (8×8 cm) were assessed without further magnification by three investigators without knowledge of the patients' glucose tolerance.

Results

Ophthalmological examination in all subjects disclosed normal visual acuity (0·7–1·0) and intraocular pressure and clear ocular media. Retinal vascular changes were limited to slight attenuation of arterioli and pathological arteriovenous crossings in 18 subjects over 50 years of age, equally distributed between the subgroups and controls. No apparent retinal disease was found by ophthalmoscopy except for depigmentation and minor hyperpigmented lesions similar to macular degeneration.

In some subjects, detailed examinations of fluorescein angiograms and fundus colour slides showed changes of the RPE. The prevalence of these alterations—provided they were detected by both methods—is given in Table 2. RPE changes were noted in 23% of subjects with normal OGTT and in 35% of those with borderline OGTT. About half of the subjects with decreased OGTT had RPE changes (p<0·05).

These alterations of RPE were characterised on fluorescein angiograms by the following two findings: 'window' defects comprising a variety of alterations ranging from minute dots to multiple or confluent circumscribed areas; and punctate choroidal hyperfluorescence seen as solitary or multiple sharply bordered lesions, some of them looking like drusen (Figs. 1–4). The RPE changes appeared early during angiography, coinciding with the choroidal filling of dye. They showed little change with time and faded with the choroidal fluorescence. On colour fundus photographs these changes corresponded to depigmented, lightly yellow dots or spots and areas with attenuated RPE.

Table 1 *Criteria for OGTT*

Groups	*Venous blood glucose, mmol/l*		
	Fasting	*1 hr*	*2 hr*
Normal	<5·2	<7·8	<6·4
Borderline	<5·2	≥7·8 or	≥6·4
Decreased	<5·2	≥8·9 and	≥6·7

Table 2 *Prevalence of retinal changes and age of subjects*

	No. of subjects	*Retinal changes*	*Age, years (mean ± SEM)*
A. Normal controls	64	15 (23%)	43±1
B. Borderline OGTT	49	17 (35%)	43±2
C. Decreased OGTT	37	18 (49%)*	46±2

*The difference between groups A and C is significant (p<0·05), that between groups A and B is not.

Table 3 *Distribution of 150 subjects with or without retinal changes according to age (<50 and ≥50 years)*

	Age of subjects (years)	
	<50	*≥50*
Normal controls		
No changes (n=49)	40	9
Retinal changes (n=15)	3 (7%)	12 (57%)
Borderline or decreased OGTT		
No changes (n=51)	36	15
Retinal changes (n=35)	17 (32%)*	18 (55%)

*p<0·01.

The prevalence of RPE changes in subjects older than 50 years was not related to OGTT (Table 3). On the other hand in the younger groups the prevalence of RPE changes was much higher among those with borderline and decreased OGTT than in normal persons (p<0·01).

Retinal microaneurysms were found in only two subjects, both with decreased OGTT.

Discussion

The ocular changes encountered in this study were lesions of RPE, and seen as 'window' defects or drusen-like changes on fluorescein angiograms. The RPE lesions, though limited in size and number, were present in 23% of subjects with a completely

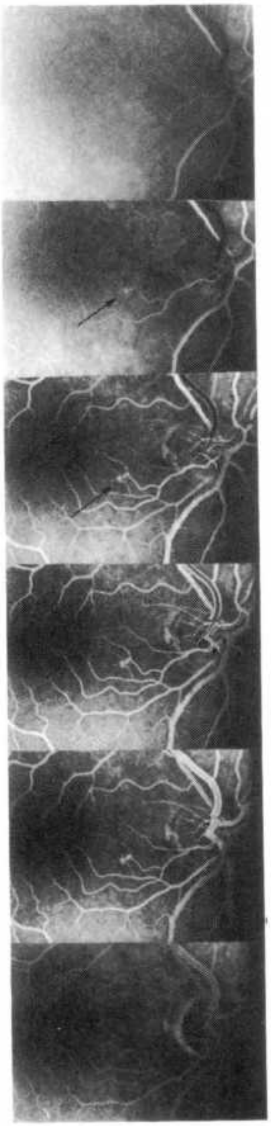

Fig. 1

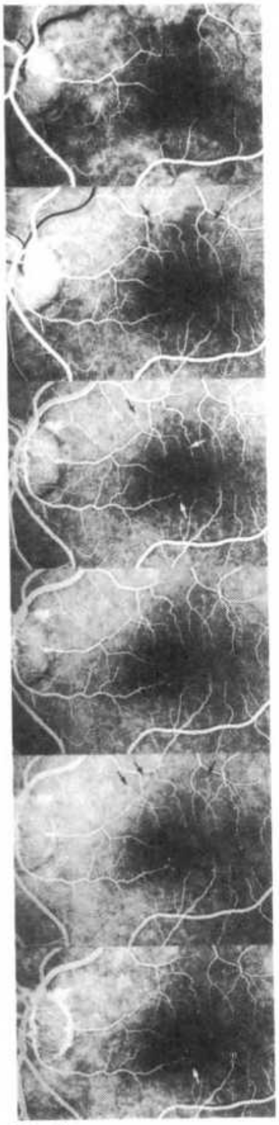

Fig. 2

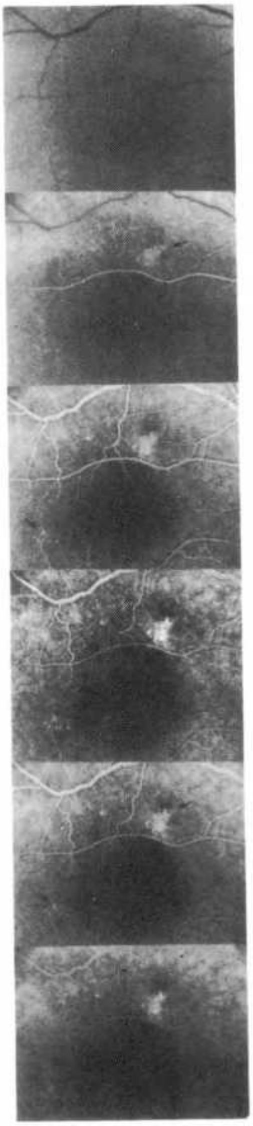

Fig. 3

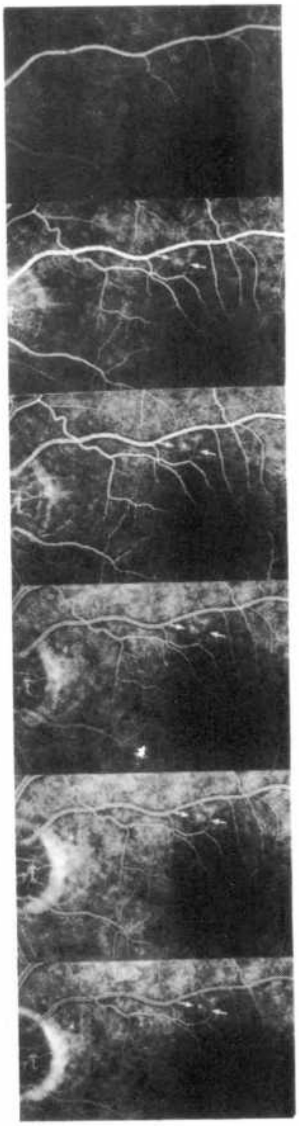

Fig. 4

Figs. 1–4. *Fluorescein angiograms in early, arteriovenous, and late phase (about 2 minutes), depicting alterations at the RPE level (arrows).* Fig. 1 *Hyperfluorescent lesion in papillo-macular area; female aged 54, borderline OGTT.* Fig. 2 *Multiple tiny drusen-like changes; female aged 40, borderline OGTT.* Fig. 3 *Hyperfluorescent spots and a confluent area of attenuated RPE above fovea; male aged 42, decreased OGTT.* Fig. 4 *Indistinctly bordered hyperfluorescent spots; male aged 47, decreased OGTT.*

normal fasting blood glucose and OGTT. This figure underestimates the incidence of these lesions, since only a 30° view of the fundus was assessed. Recently, subtle morphological elements visible both on fluorescein angiograms and colour photographs were reported in about 30% of normal subjects when a 45° view of the fundus was examined.[4] This figure, when extrapolated to a 30° view, would correspond to the 23% in our normal controls.

In subjects with borderline OGTT the incidence of RPE lesions increased to about 35% and in those with decreased OGTT to 49%. Such a trend towards a higher incidence of retinal lesions parallel with increased disturbances of glucose tolerance is supported by observations of such changes in insulin-dependent diabetics with an onset of the disease prior to the age of 40 years; patients younger than 50 years showed RPE lesions in 53%, and those who were older in 70%.[7] In a similar study the incidence of RPE lesions in juvenile diabetics was as high as 80%.[8]

In general, RPE lesions increase with age and probably proceed to senile macular degeneration.[9] However, electron microscopy has revealed initial RPE changes as early as the age of 30.[10] In the angiographic 'window' defects the RPE is attenuated, with partial or complete loss of melanin granules, and may be associated with sclerosis of the subjacent choriocapillaries.[11] RPE lesions are often accompanied by drusen, which are regarded as residual products of insufficient phagocytosis by the RPE of photoreceptor outer segments, and recognised as basal lamina deposits on Bruch's membrane.[12] Drusen are often found in diabetics[13]

The scantiness of microaneurysms (found in only two subjects) and the absence of other vascular abnormalities indicate that morphological retinal microangiopathy is rare in conditions prior to manifest diabetes.

In human diabetics increased accumulation of fluorescein into the vitreous, as shown by fluorophotometry, is an early finding which may precede angiographically detectable retinal microangiopathy.[14] In streptozotocin diabetic rats, also, an enhanced intravitreal concentration of this dye is seen very early during the disease.[15] The reason for the increased fluorescein accumulation is not clear. Fluorescein is probably eliminated from the vitreous by an active transport mechanism,[16] and several observations suggest that the RPE may be involved in this process.

Early morphological alterations of the RPE were reported in Streptozotocin-induced[17] and spontaneously diabetic rats.[18]

The fluorescein extrusion from eyes of normal and diabetic rats can be inhibited by sodium iodate, a substance that results in damage to the RPE.[19,20]

Although conclusive evidence is lacking, impaired function of the RPE may be an early change in experimental diabetes and possibly in human diabetes as well. An interesting question is whether the changes described here constitute an early retinal alteration which goes on to the microangiopathy characteristic of diabetic retinopathy. If so, the RPE changes might possibly be used as an early marker for this type of retinopathy. Only prospective studies can solve this problem. For this reason the subjects with impaired glucose tolerance with or without RPE alterations are being re-examined with regard to glucose tolerance and RPE changes.

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References

1 Soler NG, Fitzgerald MG, Maslins JM, Summers ROC. Retinopathy at diagnosis of diabetes, with special reference to patients under 40 years of age. *Br Med J* 1969; **iii:** 567–9.

2 Zetterström B, Gjötterberg M. The diagnosis of retinopathy by fluorescein angiography in latent diabetes. *Acta Ophthalmol (KGL)* 1974; **52:** 1–12.

3 Harrower ADB, Clarke BF. Diabetic retinopathy with normal glucose tolerance. *Br J Ophthalmol* 1976; **60:** 459–62.

4 Nielsen NV. The normal retinal fluorescein angiogram. *Acta Ophthalmol (KGL) 1982;* **60:** 657–70.

5 Efendic S, Wajngot A, Cerasi E, Luft R. Insulin release, insulin sensitivity, and glucose intolerance. *Proc Natl Acad Sci USA* 1980; **77:** 7425–9.

6 Reaven GM, Bernstein R, Davis B, Olefsky JM. Nonketotic diabetes mellitus: insulin deficiency or insulin resistance? *Am J Med* 1976; **60:** 80–8.

7 Jerneld B, Algvere P. The prevalence of retinopathy in insulin-dependent juvenile-onset diabetes mellitus—a fluorescein angiographic study. *Acta Ophthalmol (KGL)* 1984; **62:** 617–30.

8 Palmberg P, Smith M, Waltman S, *et al.* The natural history of retinopathy in insulin-dependent juvenile-onset diabetes *Ophthalmology* 1981; **88:** 613–8.

9 Sarks SH. Ageing and degeneration in the macular region: a clinico-pathological study. *Br J Ophthalmol* 1976; **60:** 324–41.

10 Hogan MJ. Role of the retinal pigment epithelium in macular disease. *Trans Am Acad Ophthalmol Otolaryngol* 1972; **76:** 64–80.

11 Keno DD, Green R. Retinal pigment epithelial window defect. *Arch Ophthalmol* 1978; **96:** 854–6.

12 Kornzweig AL. Ageing of the retinal pigment epithelium. In: Zinn KM, Marmor MF, eds. *The retinal pigment epithelium.* Cambridge, Mass: Harvard University Press, 1979: 478–95.

13 Yanoff M, Fine B. *Ocular pathology.* 2nd ed. Hagerstown, Philadelphia, Harper and Row: 1982: 715.

14 Cunha-Vaz JG, Goldberg MF, Vygantas C, Noth J. Early detection of retinal involvement in diabetes by vitreous fluorophotometry. *Ophthalmology* 1979; **86:** 264–75.

15 Waltman S, Krupin T, Hanish S, Oestrich C, Becker B. Alteration of the blood-retinal barrier in experimental diabetes mellitus. *Arch Ophthalmol* 1978; **96:** 878–9.

16 Blair NP, Zeimer RC, Rusin MM, Cunha-Vaz JG. Outward transport of fluorescein from the vitreous in normal human subjects. *Arch Ophthalmol* 1983; **101:** 1117–21.

17 Grimes PA, Laties AM. Early morphological alteration of the pigment epithelium in streptozotocin-induced diabetes: increased surface area of the basal cell membrane. *Exp Eye Res* 1980; **30:** 631–9.

18 Blair NP, Tso MOM, Dodge JT. Pathologic studies of the blood-retinal barrier in the spontaneously diabetic BB rat. *Invest Ophthalmol Vis Sci* 1984; **25:** 302–11.

19 Anstadt B, Blair NP, Rusin M, Cunha-Vaz JG, Tso MOM. Alteration of the blood-retinal barrier by sodium iodate: kinetic vitreous fluorophotometry and horseradish peroxidase tracer studies. *Exp Eye Res* 1982; **35:** 653–62.

20 Krupin T, Waltman SR, Szewczyk P, *et al.* Fluorometric studies on the blood-retinal barrier in experimental animals. *Arch Ophthalmol* 1982; **100:** 631–4.

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Natural history of peripheral neovascularisation in diabetic retinopathy

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SUMMARY A study of 62 untreated eyes of 54 diabetic patients with peripheral neovascularisation is reported. The study shows that neovascularisation rarely remains confined to one sector of the retina; 18% of eyes had developed disc new vessels within one year, 27% had a vitreous haemorrhage within five years, and 10% developed either macular traction or a retinal detachment.

Peripheral neovascularisation in diabetic retinopathy is considered to have a benign prognosis as opposed to disc neovascularisation, in which the prognosis is unfavourable.[1] The present study was therefore conducted to determine the likely outcome, without treatment, in eyes with peripheral new vessels, which in contrast to disc new vessels (NVD) are also known as new vessels elsewhere (NVE).[2] Events recorded were the progression of NVE in each retinal quadrant ('by sector'), the development of disc new vessels, vitreous haemorrhage, and retinal detachment.

Patients and methods

The study included 62 eyes of 54 diabetic patients with NVE, all of whom were attending the Hammersmith Hospital Diabetic Retinopathy Clinic during 1965–83. The criterion for inclusion was the clinical diagnosis of one or more areas of NVE, confirmed on colour photography and/or fluorescein angiography. Excluded were eyes with new vessels on or within one disc diameter of the optic disc, and those considered to have intraretinal microvascular abnormalities (IRMA) alone. Also excluded were eyes that had received photocoagulation or patients who had undergone pituitary ablation. Assessment was made by annual clinical examination and colour fundus photography, with fluorescein angiography at diagnosis and thereafter approximately biannually. Clinical details included best corrected visual acuity, slit-lamp biomicroscopy, and fundal examination by direct and indirect ophthalmoscopy, under mydriasis, by the staff of the Diabetic Retinopathy Clinic. Visual acuity was scored 1–12 between 6/6 on the Snellen chart to no perception of light (NPL). Snellen acuities of 6/6–6/60 were scored 1–7, V/As 3/60-NPL were scored 8–12 (8=3/60, 9=counting fingers, 10=hand movements, 11=perception of light, 12=no perception of light). Photographic documentation was obtained by a method of standard photographic survey, as defined by Oakley *et al.*[3] using a 30° field of the Zeiss (Oberkocken) fundus camera. For the purpose of this assessment the retina was divided into four sectors (upper temporal, lower temporal, upper nasal, lower nasal) by a horizontal and vertical line bisecting the optic disc. Where a single area of neovascularisation was crossed by these lines, grading was limited to the predominant sector affected. Progression of NVE was assessed by the development of new vessels in separate sectors of the retina. Grading change in a single area or the development of a separate area within the same sector was not considered. Most patients were studied prior to the value of photocoagulation in diabetic retinopathy being established.

There were 29 males (54%) and 25 females (46%). Thirty-one (57%) had insulin dependent diabetes (IDDM) and 23 (43%) had non-insulin dependent diabetes (NIDDM). The mean duration of diabetes to diagnosis of NVE in those with IDDM was 16·6 years (SD 8·8; range 4–41), with mean age of onset of diabetes 21·8 years (SD 10·5; range 5–46). In those with NIDDM, the duration of known diabetes to NVE formation was 7·2 years (SD 6·5; range 0–25), with a mean age of onset 50·1 years (SD 8·3; range 32–62). The mean duration of follow up was 4·8 years (SD 2·6; range 1–11). Twenty-nine eyes of 28 patients were followed up for a period of at least five years. Among the remaining 26 patients the period of observation was terminated by death in 12 patients

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Table 1 *Percentage of eyes, grouped according to number of sectors containing NVE, at each year of follow-up*

No. of sectors	*Year*					
	0	*1*	*2*	*3*	*4*	*5*
1	45	24	20	18	17	15
2	26	31	27	23	17	15
3	24	32	31	29	27	11
4	5	11	16	16	17	29·5
ng	0	2	6	14	22	29·5
Total	100	100	100	100	100	100

ng=Not gradable owing to complications, for example, vitreous haemorrhage.

(14 eyes) after a mean follow up 2·8 years (SD 1·2; range 1–4), and four patients (four eyes) were lost to follow-up after a mean of 1·5 years (SD 0·6; range 1–3) years. As a result of reports concerning the efficacy of photocoagulation[24] it was considered unethical to withhold this treatment after 1978 in eyes with progressive retinopathy. Thus 15 eyes of 14 patients (of whom four died before five years of follow-up was completed) were treated after a mean follow-up of 2·7 years (SD 1·2; range 1–4), and thereafter excluded from the present study.

Results

PROGRESSION OF NVE

A steady progression of NVE in other areas of the retina is demonstrated in Table 1. Of the 28 eyes with one sector alone involved at diagnosis in only two (7%) did the new vessels remain limited to that sector after five years, although in an additional two (7%) eyes the new vessels had regressed. NVE had developed in at least one further sector in 15 of 28 (54%) within one year, and at five years seven of 16 (44%) had new vessels in four sectors or were ungradable owing to complications. Of the whole group 44 of 62 (71%) at diagnosis had NVE confined to one or two sectors only, progressing to 16 of 27 (59%) with NVE in four sectors or ungradable owing to complications at five years (Fig. 1).

DEVELOPMENT OF DISC NEW VESSELS

In the whole group 24 out of 62 eyes (39%) developed disc new vessels (NVD) after a mean duration of follow-up of 2·3 years (SD 1·3; range 1–6) from diagnosis of NVE alone (Fig. 2; Table 2). At one year NVD had already developed in 11 eyes (18%). NVE

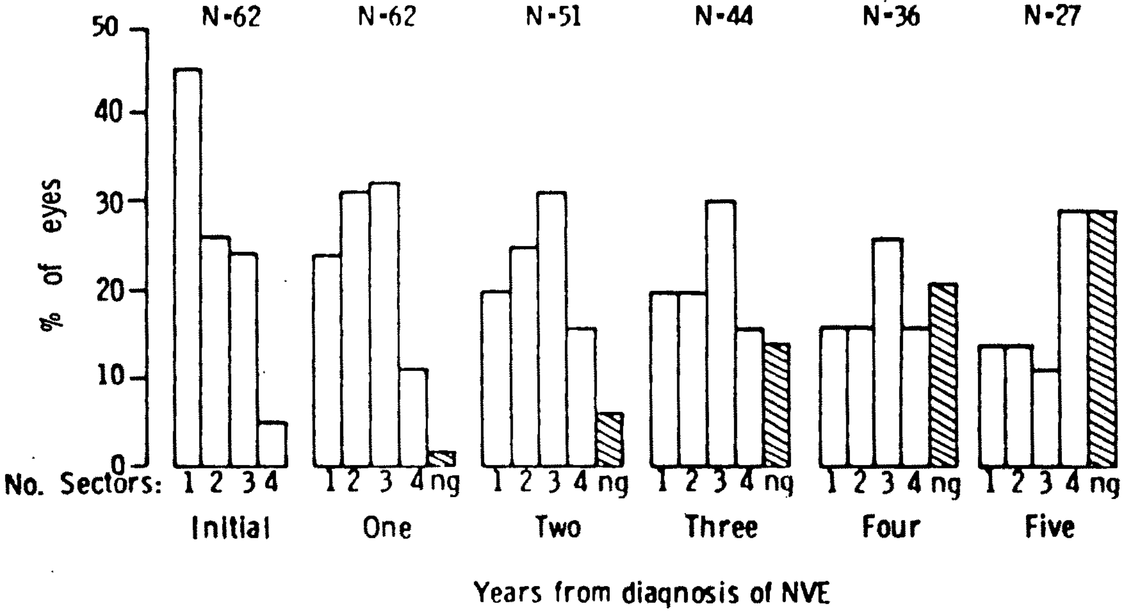

Fig. 1 *The number of sectors containing new vessels elsewhere (NVE) at each year of follow-up expressed as a percentage of the whole group (ng=not gradable).*

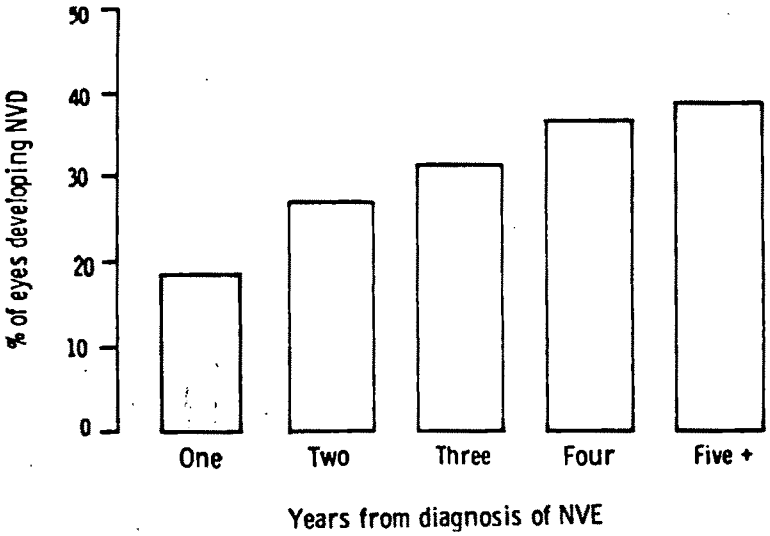

Fig. 2 *The percentage of eyes developing disc new vessels (NVD) at each year of follow-up (five+ =five or more).*

were present in three or four sectors of the retina in 18 of 24 eyes (75%), in two sectors in four of 24 (17%), and in one sector only in two of 24 (8%) at the time of development of NVD.

Table 2 *Development of disc new vessels*

	Year of follow-up				
	1	*2*	*3*	*4*	*5+*
No. of eyes with NVD	11	17	20	23	24
% of eyes with NVD	18	27	32	37	39

VITREOUS HAEMORRHAGE

Vitreous haemorrhage (VH) occurred in 17 eyes (27%) after a mean follow-up of 2·8 years (SD 1·5; range 1–7) (Fig. 3, Table 3). The mean age at the time

Table 3 *Occurrence of vitreous haemorrhage*

	Year of follow-up				
	1	*2*	*3*	*4*	*5+*
No. of eyes with VH	5	9	12	13	17
% of eyes with VH	8	14	19	21	27

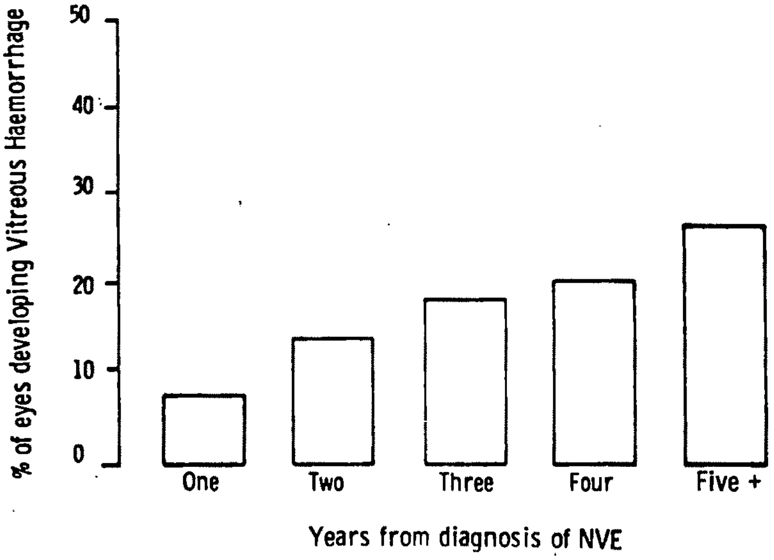

Fig. 3 *The percentage of eyes developing a vitreous haemorrhage at each year of follow-up (five+ =five or more).*

of haemorrhage was 51·8 years (SD 13·8; range 29–75). The visual acuity was reduced by a mean score of 3·7 in 15 of 17 (88%). Of these, 60% (9 of 15) made no spontaneous visual recovery, and 40% (6 of 15) recovered a mean score of 2·7, within one year. Within a further year three of these had lost vision owing to rebleeding. In two eyes (12%) VH occurred without an objective deterioration in the visual acuity. Those with localised subhyaloid haemorrhage were not included. At the time of haemorrhage seven of 17 (41%) had NVE alone, whereas 10 of 17 (59%) had developed NVD.

FIBROSIS; MACULAR TRACTION; RETINAL DETACHMENT

The development of fibrous tissue in association with NVE occurred in 25 of 62 (40%) eyes, after a mean follow-up of 2·3 years (SD 2·2; range 0–3) from diagnosis of NVE. Of the whole group eight of 62 (13%) developed tractional complications; of these, three of eight (37%) had macular traction alone, and five of eight (63%) developed a retinal detachment. No distinction could be made between rhegmatogenous and traction detachment alone, and details of the extent and rate of progression have not been investigated. The mean follow-up from diagnosis of NVE was 3·7 years (SD 1·4; range 2–6), with a mean duration of associated fibrous tissue, before detachment, of 2·5 years (SD 1·4; range 1–5).

VISUAL ACUITY

Forty-two of 62 eyes (68%) started the study with a visual acuity of 6/6 or better. In 13 of 62 (21%) vision was between 6/9 and 6/18, and in seven eyes (11%) it was between 6/24 and 6/60. Initial visual loss was attributable to diabetic macular disease in 18 of 20 (90%), owing to lens opacity in one (5%) and amblyopia in one (5%). After a mean follow-up of 4·8 years (SD 2·6; range 1–11) acuity had deteriorated in 27 eyes (44%) by a mean score of 4·3 (SD 2·6). Acuity was then 6/6 or better in 29 of 62 eyes (47%), between 6/9 and 6/18 in 11 eyes (18%), between 6/24 and 6/60 in nine eyes (14%), and worse than 6/60 in 13 eyes (21%) (Fig. 4). Of the 27 eyes which deteriorated, visual loss was attributed to diabetic macular disease in 13 (49%), to vitreous haemorrhage alone in five (18%), to tractional complications with or without vitreous haemorrhage in eight (29%), and to thrombotic glaucoma with vitreous haemorrhage in one (4%).

Discussion

The predominance of proliferative retinopathy in younger diabetics with IDDM[5] is reflected in the study population (57%). It is, however, notable that 43% had NIDDM with a mean age of onset of 50·1 years, confirming the increasingly recognised fact that neovascular retinopathy is also important in this older age group.[6,7] That new vessels are diagnosed after a shorter duration of known diabetes in patients with NIDDM (a mean of 7·2 years after diagnosis of diabetes as opposed to 21·7 years in those with IDDM) may reflect a prolonged subclinical disease state in the former group.

In the group of patients studied neovascularisation

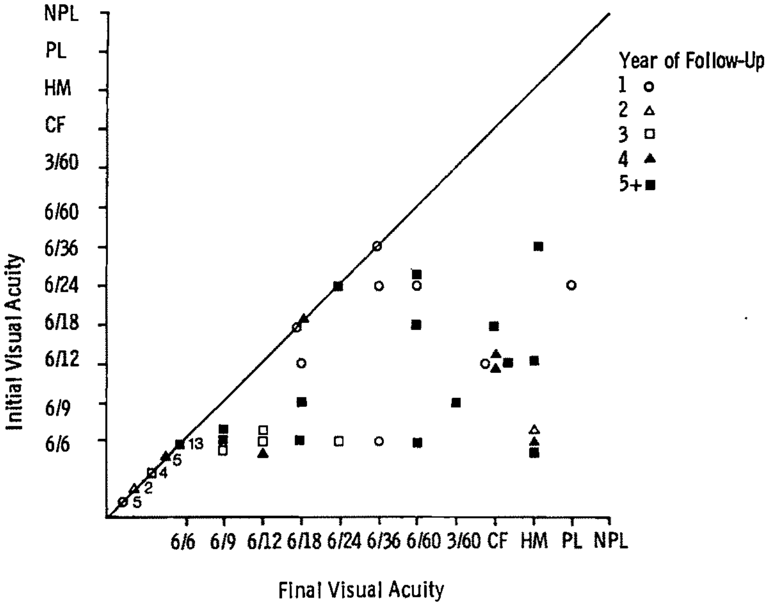

Fig. 4 *Initial and final visual acuity. Eyes are represented by a symbol denoting duration of follow-up in years (5+=5 or more), individually, or grouped with the number in each indicated. Diagonal: No change line. CF=counting fingers. HM=hand movements. PL=perception of light. NPL=no perception of light.*

rarely remained confined to the initial sector or sectors affected. This presumably reflects the generalised nature of the underlying microangiopathy and resultant capillary closure. It was not possible to study the extent of peripheral capillary closure, as initial fluorescein angiograms did not incorporate a peripheral survey. This progression implies that local or sector treatment may not be adequate, particularly where careful follow-up cannot be assured.

The development of NVD in 18% of eyes at one year is similar to that found in a comparable group of eyes by the Diabetic Retinopathy Study Research Group.[4] In the control group of eyes with NVE alone in the British Multicentre Trial of Photocoagulation[8] 50% developed NVD within five years as opposed to 37% in the present study. These two controlled clinical trials[8 9] have demonstrated unequivocally the benefits of photocoagulation for NVD, though the results for treatment for NVE alone have been less clear. The British Multicentre Group[8] were unable to demonstrate a statistically significant difference between control and treated eyes with NVE alone over a five-year period, despite the high percentage that developed NVD. In the USA the Diabetic Study Research Group[9] could not recommend a clear choice between prompt photocoagulation and deferral in this group of patients, provided high-risk characteristics[4] such as preretinal or vitreous haemorrhage were not present. In the present study 27% of eyes developed a vitreous haemorrhage, of which 50% did not make any spontaneous visual recovery, 40% developed fibrosis associated with NVE, and 10% developed retinal tractional complications, when left untreated. Why there should be no difference between treatment and no treatment in the British study, especially when 50% of the control group developed NVD, is not clear, but it is probably due to the fact that, after 1977, eyes that developed NVD in the control group were treated.

The present study indicates that peripheral neovascularisation can result in serious complications, which may preclude photocoagulation. Therefore treatment should probably be undertaken immediately, unless frequent follow up can be assured. Some authorities advocate focal or sectorial treatment initially[10] associated with careful follow-up. In view of the likely development of NVE in other sectors, and the greater recurrence of NVE following sector treatment as opposed to panretinal photocoagulation (PRP),[11] the latter may be more appropriate, particularly if follow-up cannot be assured.

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References

1 Deckert T, Simonsen SE, Poulsen JE. Prognosis of proliferative retinopathy in juvenile diabetes. *Diabetes* 1967; **16:** 726–33.

2 The Diabetic Retinopathy Study Research Group. Preliminary report on the effects of photocoagulation therapy. *Am J Ophthalmol* 1976; **81:** 383–96.

3 Oakley NW, Hill DW, Joplin GF, Kohner EM, Fraser TR. Diabetic retinopathy. 1. The assessment of severity and progress by comparison with a set of standard photographs. *Diabetologia* 1967; **3:** 402–5.

4 The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of Diabetic Retinopathy Study Findings. *Ophthalmology (Rochester)* 1978; **85:** 82–106.

5 Bodansky HJ, Cudworth AG, Whitelocke RAF, Dobree JH. Diabetic retinopathy and its relation to type of diabetes: review of a retinal clinic population. *Br J Ophthalmol* 1982; **66:** 496–9.

6 British Multicentre Study Group. Photocoagulation for diabetic maculopathy: a randomised controlled clinical trial using the xenon-arc. *Diabetes* 1984; **32:** 1010–6.

7 Klein R, Klein B, Moss S, Davis M, DeMets D. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: III: Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 1984; **102:** 527–32.

8 British Multicentre Study Group. Photocoagulation for proliferative diabetic retinopathy: a randomised controlled clinical trial using the xenon-arc. *Diabetologia* 1984; **26:** 109–15.

9 The Diabetic Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy. Diabetic Retinopathy Study Research Group report No: 8. *Ophthalmology (Rochester)* 1981; **88:** 583–600.

10 Hamilton AMP, Blach RK, Whitelocke R. Management of proliferative diabetic retinopathy. In: Kanski JJ, Morse PJ, eds. *Disorders of the vitreous retina and choroid.* London: Butterworths, 1983: 104–6.

11 Inglesby DV, Turner GS, Schulenburg WS, Kohner EM. Photocoagulation for peripheral neovascularisation in diabetes. *Br J Ophthalmol* 1985; **69:** 157–61.

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Mydriatic drugs for diabetic patients

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SUMMARY A comparative study in healthy subjects and diabetic patients of the mydriatic response to topical tropicamide 0·5% with and without added phenylephrine 10% is reported. The findings indicate that diabetic pupils respond relatively poorly to tropicamide alone but adequately and completely to the drug combination. The pupils of diabetic patients whose eyes had previously received laser treatment dilated less than those from untreated eyes by a small but significant extent. This combination of drugs is recommended for all diabetic patients to provide an adequate mydriasis with a minimum of postclinic accommodative paralysis.

It is well known that the diabetic pupil dilates poorly to standard anticholinergic eye drops.[1] This often results in application of excessive dosage of the more powerful agents such as cyclopentolate and homatropine, which leaves visual accommodation paralysed for several days.[2] The finding that the sympathetically denervated small pupil of diabetic patients is supersensitive to sympathomimetics[3 4] suggests an alternative approach. A combination of the sympathomimetic phenylephrine to ensure adequate dilatation with the rapidly acting anticholinergic tropicamide[5] to abolish the light reflex should provide a regimen to which the diabetic pupil is particularly sensitive with the minimum accommodative loss. This study has tested the efficacy of this combination in normal persons and diabetic patients, half of whom had previously undergone laser treatment for proliferative retinopathy.

Material and methods

Twenty healthy subjects (13 male, 7 female) aged 31–62 years and 41 diabetic patients (22 male, 19 female) aged 17–70 years voluntarily took part in the investigation. Many of the patients, who were unselected for type or treatment of diabetes, had diabetic eye disease and were attending the Department of Ophthalmology for observation and/or treatment of retinopathy. Twenty-four of these patients had previously received argon laser photocoagulation treatment to one or both eyes.

Pupil diameters were measured in the dark and under continuous bright illumination by infrared television pupillography.[6] This illumination, from two strip lamps placed 50 cm from the patient, was of an intense brightness comparable to that needed for ophthalmic practice. Pupils were measured before and after application of mydriatic eyedrops: tropicamide 0·5% and phenylephrine 10% (Minims, Smith and Nephew Pharmaceuticals).

Two mydriatic regimens were tested. In the first regimen 2 drops of tropicamide alone were given to one eye of all the subjects, and the peak effects were measured 30 min after instillation. Pilot experiments had shown that light reflex inhibition had reached a maximum at that time in all subjects. In the second regimen the same application of tropicamide was preceded by instillation of 2 drops of phenylephrine 30 min previously. This timing was chosen because the peak mydriatic effects of phenylephrine are reached in about twice the time taken by tropicamide.[5 7] This regimen was tested in 14 healthy and 33 diabetic subjects. As with the first regimen, measurements were made 30 min after tropicamide.

The results of the experiments were evaluated by standard statistical methods. There was no significant age difference between the three groups studied (normals, diabetic patients with and without laser treatment) within or between the two drug regimens. The study received ethical approval from the Research (Endowments) Committee of West Lambeth Health Authority.

Results

Pupil diameters before and after each treatment are illustrated in Fig. 1. Before instillation of mydriatics the diabetic pupils were smaller in darkness than the

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healthy pupils (p<0·001) and those of eyes with previous laser treatment smaller than those without (p<0·001). Under bright light the pupils of diabetics were no smaller than those of healthy subjects, irrespective of prior laser treatment. Thus prior to eye drops the difference in size between the diabetic and the healthy pupil was apparent only when measured in darkness.

After tropicamide alone the diabetic pupils dilated to a smaller final diameter than the healthy pupils (p<0·001), the difference being greater in those eyes previously exposed to laser treatment (p<0·001). Thus the healthy pupils dilated to 7·59±0·18 mm (mean ± SEM), those from the untreated diabetic eyes to 6·58±0·17 mm, and those from the laser-treated eyes to only 5·88±0·21 mm.

After phenylephrine plus tropicamide the pupil diameters were larger than after tropicamide alone in all subjects. Diabetic pupils of eyes not exposed to laser treatment dilated to the same final diameter as healthy pupils (7·99±0·16 mm and 8·21±0·17 respectively). Those of eyes previously exposed to laser treatment dilated to a slightly smaller mean diameter of 7·53±0·19 mm (p<0·05). In all diabetic patients the increment in diameter produced by addition of phenylephrine to the tropicamide treatment was significantly greater than in healthy subjects.

Small light reflex responses to illumination were observed in some (particularly the healthy) subjects following both mydriatic regimens (Table 1). These residual responses to the intense light stimulation used were always minimal and were insignificant in the diabetic patients tested with the combination regimen.

Multiple regression analysis showed that the final pupillary diameters after either regimen in healthy and diabetic subjects were uninfluenced by age, sex, or eye colour differences.

Discussion

This study has shown that the diabetic pupil fails to dilate normally to darkness, particularly in those eyes previously treated with laser photocoagulation. This failure of dilatation has been shown to be due, at least in part, to a sympathetic dysfunction related to the autonomic neuropathy of these patients.[4] The diabetic pupil also failed to dilate adequately to tropicamide eye drops. The addition of phenylephrine, which utilises the denervation supersensitivity of the small diabetic pupil, greatly improved the mydriatic drug response in diabetic patients. Quantitatively this improvement averaged 1·41 mm and 1·65 mm in the untreated and laser-treated eyes respectively and thus is of great value clinically.

Tropicamide 0·5% was effective at 30 min in

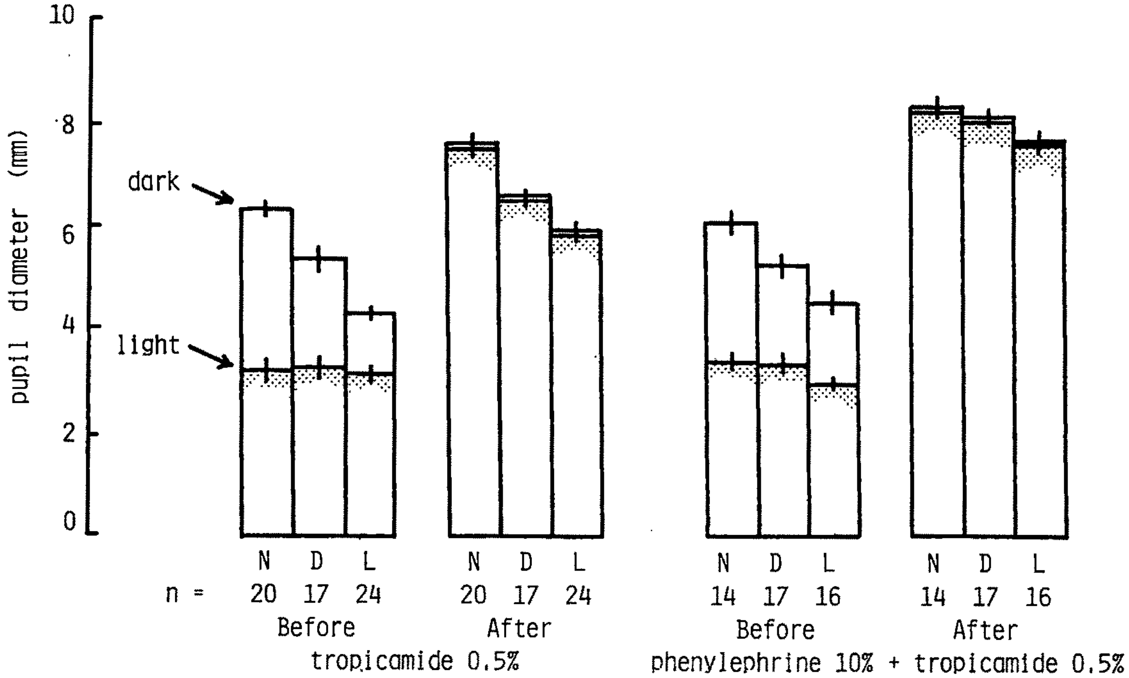

Fig. 1 *Pupil diameters in darkness and in light before and after instillation of mydriatic eyedrops.* N=*healthy subjects;* D=*diabetic eyes without laser treatment;* L=*diabetic eyes with prior laser treatment.*

Table 1 *Numbers of healthy and diabetic subjects with residual light responses (mm) after instillation of tropicamide 0·5% or phenylephrine 10% + tropicamide 0·5%*

	Total *n*	*Response (mm)*						*p**
		0–0·1	*<0·2*	*<0·3*	*<0·4*	*<0·5*	*<0·6*	
Tropicamide								
Healthy	20	11	3	1	1	1	3	<0·01
Diabetic	41	30	5	5	1			<0·05
Phenylephrine + tropicamide								
Healthy	14	10	3	0	0	1		<0·05
Diabetic	33	25	6	2				NS

*Significance of difference of group mean from zero.

antagonising the light reflex response to the intensely bright light used, which was comparable to the intensity of light necessary in ophthalmic practice. This fast-acting anticholinergic drug was preferred to stronger agents such as cyclopentolate or homatropine to avoid the prolonged accommodative paralysis that occurs with these agents. There were no reports of subjective discomfort with either regimen. As neither glare nor accommodative problems occurred, we did not consider reversal with miotic drops, which can themselves cause discomfort.

Our findings do, however, indicate that pupils of diabetic patients who have had laser treatment for proliferative retinopathy are especially difficult to dilate, even with the combined mydriatic regimen. It is known that the pupillary signs of diabetes are more marked in patients with proliferative compared with background retinopathy.[3] Thus it is not clear whether laser treatment per se, or a more advanced stage of diabetic eye disease, makes the pupil more resistant to mydriatics. However, from the practical point of view the combination regimen did satisfactorily dilate the pupil to 7·5 mm in the light in these laser-treated eyes.

In conclusion, the combination of phenylephrine and tropicamide provides a very effective and comfortable mydriasis for fundal inspection in the diabetic patient.

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References

1 Ohrt V. Diabetic iridopathy. *Dan Med Bull* 1968; **15:** 244–8.

2 Dornan TL, Peckar CO, Steemson JM, Hockaday TDR. Clinic screening for retinopathy – which dilating drops? *Diabetologia* 1981; **20:** 7.

3 Hayashi M, Ishikawa S. Pharmacology of pupillary responses in diabetes – correlative study of the responses and grade of retinopathy. *Jpn J Ophthalmol* 1979; **23:** 65–72.

4 Smith SA, Smith SE. Evidence for a neuropathic aetiology in the small pupil of diabetes mellitus. *Br J Ophthalmol* 1983; **67:** 89–93.

5 Smith SE. Mydriatic drugs for routine fundal inspection. *Lancet* 1971; **ii:** 837–9.

6 Smith SE, Smith SA, Brown P, Fox C, Sonksen PH. Pupillary signs in diabetic autonomic neuropathy. *Br Med J* 1978; **ii:** 924–7.

7 Gambill HD, Ogle KN, Kearns TP. Mydriatic effect of four drugs determined with pupillograph. *Arch Ophthalmol* 1967; **77:** 740–6.

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Outward transport of fluorescein from the vitreous in aphakic eyes

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SUMMARY By administering fluorescein intravenously to 95 patients we calculated the ratio of fluorescein concentration in the vitreous at the time of its peak level compared with the estimated unbound concentration of fluorescein in the plasma at the same time. We studied 12 normal phakic and 83 aphakic eyes approximately two months, one year, and more than two years after cataract extraction. All the eyes had undergone intracapsular cataract extraction or extracapsular cataract extraction, with or without posterior capsulotomy, because of senile cataract. The calculated ratio in patients with intracapsular and extracapsular lens extraction was statistically significantly reduced at two months and one year after cataract extraction and was normalised at more than two years after the operation in comparison with normal subjects. The ratio was statistically significantly reduced in patients with intracapsular extraction compared with those with extracapsular extraction at two months and one year after surgery. Posterior capsulotomy had no effect on the ratio. The ratio, we considered, at least partially reflects the outward transport of fluorescein from the vitreous cavity. Although the findings reflect subclinical phenomena, they are of importance when considering postoperative sequelae. The posterior lens capsule, zonule, and intact anterior vitreous face may be essential for the anterior uvea to function in the outward transport of fluorescein from the vitreous cavity.

Recently the basic surgical technique in cataract extraction has been changing from intracapsular to extracapsular, because with the extracapsular method there is a lower incidence of such postoperative complications as cystoid macular oedema, vitreous changes, and retinal detachment.[1 2] Although an intact posterior lens capsule postoperatively has been regarded as essential in preventing these complications, its biological significance is unknown.

Worst[3] has postulated that the aqueous becomes biotoxic after cataract extraction, and stressed the significance of the intact posterior lens capsule and vitreous as a protective factor against aphakic cystoid macular oedema. Ozaki[4] has stated that the posterior lens capsule may serve as a diffusion barrier of some substances. A common feature of these hypotheses is that, when the posterior lens capsule is lost after intracapsular cataract extraction, substances in the aqueous penetrate more easily into the vitreous cavity and affect the retina.

More recently Binkhorst[1] explained the postoperative disorders following intracapsular cataract extraction by the term 'barrier deprivation syndrome.'[1] He suggested that intracapsular cataract extraction deprives the eye of the stabilising effect of the lens-zonule barrier and causes loss of stability inside the eye—namely, endophthalmodonesis, whose mechanical aspects may be the cause of postoperative complications. The biological nature of this mechanical aspect is unknown.

Studies with fluorophotometry have shown a disruption of the blood-retinal barrier following lens extraction that was greater after intracapsular than after extracapsular extraction.[5 6] These authors have considered that the high concentration of fluorescein in the vitreous is mainly due to hyperpermeability of the dye from the blood to the vitreous. Is that assumption true? Fluorescein is actively transported from the vitreous into the blood,[7 8] and this function seems to be disturbed in some pathological con-

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ditions.[9-11] Furthermore, Blair and associates[12] have recently demonstrated in healthy persons that the outward permeability to fluorescein was approximately 30 times the inward permeability. Exchange of the dye between the vitreous and the blood occurs across several cellular layers, which constitute the blood-vitreous barrier. These layers include the retinal pigment epithelium, retinal vascular endothelium, non-pigmented ciliary epithelium, and irideal pigment epithelium.[7 8 13-15] Among the sites of the function the non-pigmented ciliary epithelium and the irideal pigment epithelium are in the vicinity of the lens; they are assumed to be influenced by surgical traumas of lens extraction and also by whether or not the posterior lens capsule remains intact in the postoperative eye.

We measured the ratio between the outward and inward coefficients of permeability to fluorescein in normal subjects, and in subjects who underwent intracapsular cataract extraction, extracapsular cataract extraction, and extracapsular cataract extraction with posterior capsulotomy. We discuss here the possible role of the posterior lens capsule, especially its relationship to the active transport of fluorescein from the vitreous cavity.

Subjects and methods

SUBJECTS

At approximately two months, one year, and more than two years (average of 3·9 years) after cataract extraction we randomly selected 20 cases each that underwent intracapsular and extracapsular procedures, and 15 cases that underwent extracapsular extraction and posterior capsulotomy at one session by cystotome or immediately after original surgery by YAG (yttrium-aluminium-garnet) laser. The capsulotomy was not large enough to allow a large amount of the vitreous to herniate into the anterior chamber. All the subjects underwent the operation because of senile cataract. The subjects examined at the three time periods were not the same. All patients were told the nature of the study, and all gave their informed consent.

We then excluded from the study cases that had operative complications such as vitreous loss or endophthalmitis, and ocular disorders associated with disruption of the blood retinal barrier such as uveitis, systemic hypertension requiring therapy, diabetes mellitus, pigmentary retinal dystrophy, and degenerative myopia. Patients under 55 years old and those who had disorders of the kidney or liver, or who could not come for the examinations, were also excluded from the study. Twelve normal volunteers over 55 years old were included in the study. The distribution of cases and eyes that were actually studied is shown in Table 1. There were no statistically significant differences among the groups.

Table 1 *Distribution of eyes studied*

Group	*Time after operation*	*No. of eyes*	*Age range (yr)*	*Average age (yr±SD)*	*Number and sex*
Normal		12	57–70	67·21±7·14	5M/7F
ICCE*	2 mo	13	56–74	68·39±6·19	5M/8F
ECCE*	2 mo	15	55–79	66·34±8·21	5M/10F
ECCE.PC*	2 mo	11	55–79	65·76±5·46	6M/5F
ICCE	1 yr	11	60–80	69·34±6·62	6M/5F
ECCE	1 yr	12	55–80	67·82±7·52	5M/7F
ICCE	>2 yr	11	55–74	67·44±6·51	6M/5F
ECCE	>2 yr	10	58–76	64·52±7·32	5M/5F

*ICCE, intracapsular cataract extraction; ECCE, extracapsular cataract extraction; ECCE.PC, extracapsular cataract extraction with posterior capsulotomy.

METHODS

The theoretical basis of the methodology is the same as described by Blair and associates.[12] The new aspect in this study is that fluorescein was administered intravenously. To measure the fluorescein concentration in the vitreous, we used commercially available fluorophotometers[13-18] (Fluorotron Master, Coherent Co., CA, and Gamma-Inami Fluorophotometer, Inami Co., Tokyo, Japan). During the examination with the Fluorotron Master, which is also capable of measuring fluorescein concentrations in the serum, aphakic patients wore glasses or contact lenses, and all patients were examined under a fully mydriatic pupil.

Each subject was given 10 mg/kg sodium fluorescein intravenously. Fluorescein fundus angiography was done to detect cystoid macular oedema. Vitreous fluorophotometry was performed hourly for seven or eight hours, in most cases starting one hour after the patient received the fluorescein by the method described previously.[17 18] From the results of serial fluorophotometry we recognised the peak concentration of fluorescein in the mid vitreous (9 mm from the retina) (Cv) and the time of the peak concentration. Blood was obtained from a finger prick both at one hour after administration of fluorescein and at the end of the measurement series. The total blood concentration was also measured by fluorophotometry and was plotted as a function of time. The value at the time of maximum Cv (Ct) was interpolated according to an exponential decline. Then the concentration of unbound fluorescein in the serum at time t (Cs) was calculated from the following equation, as described by Blair and associates[12]:

$$Cs=\%UCt/100\text{-}Hct,$$

where %U is the percentage of unbound fluorescein in the serum (as %U, 17·5% was used according to the results by Araie *et al.*[19]) and Hct is the haematocrit (45% for males, 40% for females). In some cases the Cs was measured by the above procedures and in the remainder the Cs was directly measured by ultrafiltration using membrane cone (MPS-3, Amicon Co., Tokyo, Japan) at the time of the measurement of the total blood concentration, and was plotted as a function of time. Ct was interpolated according to an exponential decline. To find the difference in the mixing rate at the long term reading between the aqueous and vitreous fluorescein among the groups we measured the ratio of the concentration of fluorescein in the aqueous (centre of the anterior chamber) at the time of maximum Cv (C_A) and Cv.

Results

Table 2 gives the time of peak Cv, Cv, Ct, Cs, Cs/Cv, and C_A/Cv for each group at the three time periods. At two months and at one year after the operation the Cs/Cv ratio was statistically significantly lower in all groups except the extracapsular group at 1 year that underwent cataract extraction than in normal subjects ($p<0\cdot01-p<0\cdot05$), and was statistically significantly lower in intracapsular than in extracapsular extraction groups ($p<0\cdot05$). There was no statistically significant difference in the Cs/Cv ratio between the group given extracapsular extraction and the group given extracapsular extraction with posterior capsulotomy ($p<0\cdot5$). More than two years after the operation there was no statistically significant difference in the Cs/Cv ratio between the intracapsular extraction and extracapsular extraction groups ($p>0\cdot5$), between the normal and intracapsular groups ($p>0\cdot5$), and between the normal and extracapsular groups ($p<0\cdot3$). There was no statistically significant difference in the Ca/Cv ratio among the groups studied ($p<0\cdot5$).

Cystoid macular oedema was detected in five eyes of the intracapsular extraction group and six eyes of the extracapsular extraction group at two months after the operation, and was detected in one eye of the intracapsular extraction group at one year after the operation. Although these cases had low Cs/Cv ratios, no statistical analysis could be done because of the small number of subjects.

Discussion

The Cs/Cv ratio reflects many biological phenomena, including the function of the blood vitreous barrier (inward and outward permeability of fluorescein), intraocular diffusion of fluorescein, metabolic factors of sodium fluorescein (fluorescein gluculonide), and others, but it mainly indicates the outward transport of fluorescein.[12]

The outward transport of fluorescein from the vitreous in aphakic eyes with apparently normal fundus was lowered until at least one year postoperatively, and was lower after intracapsular than after extracapsular cataract extraction. These results are noteworthy when one considers the biology of lens extraction procedures and the pathogenesis of postoperative complications.

Miyake,[5,6] examining longstanding aphakic eyes by means of vitreous fluorophotometry, has reported an abnormally high concentration of fluorescein and a more persistent disruption of the blood retinal barrier than expected. He found a higher incidence of this disruption in aphakic eyes after intracapsular than after extracapsular cataract extraction. What is the true nature of this barrier disruption? In the present study we have shown that the persistently high concentration of fluorescein in the vitreous is partly due to the reduction of outward transport. The active transport system to sodium fluorescein inside the eye is located in the retinal pigment epithelium,

Table 2 *Fluorescein concentrations in serum and vitreous*

Group	*Time after operation*	*Time of peak Cv, hours (mean±SD)*	*Cv ng/ml (mean±SD)*	*Ct ng/ml (mean±SD)*	*Estimated Cs, ng/ml (mean±SD)*	*Cs/Cv (mean±SD)*	*Ca/Cv (mean±SD)*	*Statistical significance of Cs/Cv (t test)*	
								v. Normal	*ICCE v. ECCE*
Normal		5·42±1·44	15·64±3·48	1135·60±575·04	347·83±176·63	27·45±19·63	1.36±0·44		
ICCE*	2 mo	6·08±1·32	44·62±24·48	1414·54±494·19	396·23±153·79	9·06±5·06	1·42±0·63	p<0·01	p<0·05
ECCE*	2 mo	6·33±1·80	29·00±12·93	1245·67±266·34	389·60±85·19	13·73±5·90	1·51±0·52	p<0·05	†
ECCE.PC*	2 mo	6·01±1·42	30·12±11·26	1322·55±251·56	395·26±111·26	14·12±6·41	1·44±0·32	p<0·05	
ICCE	1 yr	6·64±0·92	32·91±9·60	1203·73±340·88	365·91±105·86	11·54±3·35	1·53±0·52	p<0·02	p<0·05
ECCE	1 yr	5·75±1·06	24·43±8·33	1385·25±388·74	391·62±98·82	15·74±4·34	1·43±0·62	p<0·1	
ICCE	>2 yr	5·82±0·87	16·18±7·80	1209·36±308·80	372·09±105·12	27·34±11·69	1·39±0·62	p>0·5	p>0·5
ECCE	>2 yr	5·80±1·03	17·00±9·01	1201·70±253·01	373·60±85·96	27·45±19·63	1·45±0·26	p<0·3	

*ICCE, intracapsular cataract extraction; ECCE, extracapsular cataract extraction; ECCE.PC, extracapsular cataract extraction with posterior capsulotomy.

†p>0·5.

retinal vascular endothelium, ciliary non-pigment epithelium, and iris pigment epithelium.[7 8 13–15] The anatomical or topographical difference in postoperative aphakic eyes following intracapsular and extracapsular cataract extraction is the existence of a posterior lens capsule and, in the former eyes, changes in the anterior vitreous face.

It is interesting to discuss the relationship between the site of active fluorescein transport and the anatomical and biological differences between the two basic procedures of cataract extraction. We assume that the ciliary non-pigment epithelium and the iris pigment epithelium may be protected from intra- and postoperative surgical injury by an intact posterior lens capsule. Actually, during extracapsular cataract extraction the ciliary body may be much less impaired through the zonule than it is in the intracapsular procedure, and postoperatively the posterior lens capsule may protect the anterior uvea from the mechanical and physical irritations of the vitreous gel.

In the present communication we have further demonstrated that planned and small posterior capsulotomy (as performed by YAG laser) did not significantly reduce the biological superiority of aphakic eyes that underwent extracapsular cataract extraction. Binkhorst has given the name 'barrier deprivation syndrome' to complications in aphakic eyes following intracapsular cataract extraction.[1] Although the true nature of this syndrome, especially the mechanism of barrier deprivation, is unknown, we consider that the dysfunction of active transport of fluorescein found in aphakias following intracapsular cataract extraction may point to the essential aspect of the barrier deprivation. It is therefore promising to consider the pathogenesis of postoperative complications, especially cystoid macular oedema, along the lines of the present findings.

Recent studies suggest that aphakic cystoid macular oedema is related to intraocular prostaglandin biosynthesis.[29–22] Normally prostaglandins are rapidly removed from intraocular fluid by the active transport mechanism of the anterior uvea.[23] It has also been shown that potentially harmful or nonphysiological substances such as fluorescein, cyclic AMP, antibiotics, and prostaglandins are removed in a similar manner inside the eye.[24] The present results indicate that the active transport of fluorescein is more impaired after intracapsular than extracapsular cataract extraction. It is widely accepted that the incidence of cystoid macular oedema is higher after intracapsular than extracapsular extraction.[2] From this evidence we conclude that aphakic cystoid macular oedema is closely related to dysfunction of the active transport mechanism. The number of cases with cystoid macular oedema in this study was too small to analyse; however, we are now conducting studies along these lines.

Some controversies surround the method of calculation we used.[12] However, here we discuss the chronological time course of posterior vitreous fluorescein concentration and serum-free fluorescein concentration. Near the time of peak Cv the vitreous fluorescein concentration does not noticeably change, and it even shows plateaux[25] in a small number of cases, whereas the serum fluorescein concentration decreases gradually. This change could cause substantial change in the Cs/Cv calculation. However, since this phenomenon is observed in both normal and pathological eyes, it probably does not influence the trends of this study.

References

1 Binkhorst C. Corneal and retinal complications after cataract extraction. The mechanical aspect of endophthalmodonesis. *Ophthalmology* 1980; **87:** 609–17.

2 Miami Study Group. Cystoid macular edema in aphakic and pseudophakic eyes. *Am J Ophthalmol* 1979; **88:** 45–8.

3 Worst JGF. Biotoxität des Dammerwassers. *Klin Monatsbl Augenheilkd* 1975; **167:** 376–81.

4 Ozaki L. The barrier function of the posterior capsule. *Am Intraocular Implant Soc J,* 1984; **10:** 182–4.

5 Miyake K. Blood-retinal barrier in eyes with long-standing aphakia with apparently normal fundi. *Arch Ophthalmol* 1972; **100:** 1437–9.

6 Miyake K. Blood-retinal barrier in longstanding aphakic eyes after extra- and intracapsular lens extraction. *Graefes Arch Klin Exp Ophthalmol* 1985; **222:** 232–3.

7 Cunha-Vaz JG, Maurice DM. The active transport of fluorescein by the retinal vessels and the retina. *J Physiol (Lond)* 1967; **191:** 467–86.

8 Cunha-Vaz JG, Maurice DM. Fluorescein dynamics in the eye. *Doc Ophthalmol* 1969; **26:** 61–72.

9 Jones CW, Cunha-Vaz JG, Zweig KO, Stein M. Kinetic vitreous fluorophotometry in experimental diabetes. *Arch Ophthalmol* 1979; **97:** 1941–3.

10 Krupin T, Waltman SR, Szewczyk P, *et al.* Fluorometric studies on the blood-retinal barrier in experimental animals. *Arch Ophthalmol* 1982; **100:** 631–4.

11 Anstadt B, Blair NP, Rusin MM, *et al.* Alteration of the blood-retinal barrier by sodium iodate: kinetic vitreous fluorophotometry and horseradish peroxidase tracer studies. *Exp Eye Res* 1982; **35:** 653–62.

12 Blair NP, Zeimer RC, Rusin MM, Cunha-Vaz JG. Outward transport of fluorescein from the vitreous in normal human subjects. *Arch Ophthalmol* 1983; **101:** 1117–21.

13 Shiose Y, Sears ML. Fine structural localization of nucleoside phosphatase activity in the ciliary epithelium of albino rabbits. *Invest Ophthalmol Visual Sci* 1966; **5:** 152.

14 Mazima T. Studies on retinitis pigmentosa. Part 22. Electron-microscopic observations of retinal 'ATP' are in experimental retinal degeneration treated with sodium iodate. *Nippon Ganka Gakkai Zasshi* 1966; **70:** 1424–41.

15 Maurice DM. The use of fluorescein in ophthalmological research. The Jonas S Friedenwald Memorial Lecture. *Invest Ophthalmol Visual Sci* 1967; **6:** 464–77.

16 Cunha-Vaz JG, Goldberg MF, Vygantas C, Noth J. Early detection of retinal involvement in diabetes by vitreous fluorophotometry. *Trans Am Acad Ophthalmol Otolaryngol* 1979; **86:** 264–76.

17 Zeimer RC, Blair NP, Cunha-Vaz JG. Vitreous fluorophotometry for clinical research: I. Description and evaluation of a

new fluorophotometer. *Arch Ophthalmol* 1983; **101:** 1753–6.

18 Zeimer RC, Blair NP, Cunha-Vaz JG. Vitreous fluorophotometry for clinical research: II. Method of data acquisition and processing. *Arch Ophthalmol* 1983; **101:** 1757–61.

19 Araie M, Sawa M, Nagataki S, *et al.* Aqueous humor dynamics in man as studied by oral fluorescein. *Jpn J Ophthalmol* 1980; **24:** 346–62.

20 Miyake K, Sakamura S, Miura H. Long-tern follow-up study on prevention of aphakic cystoid macular oedema by topical indomethacin. *Br J Ophthalmol* 1980; **64:** 324–8.

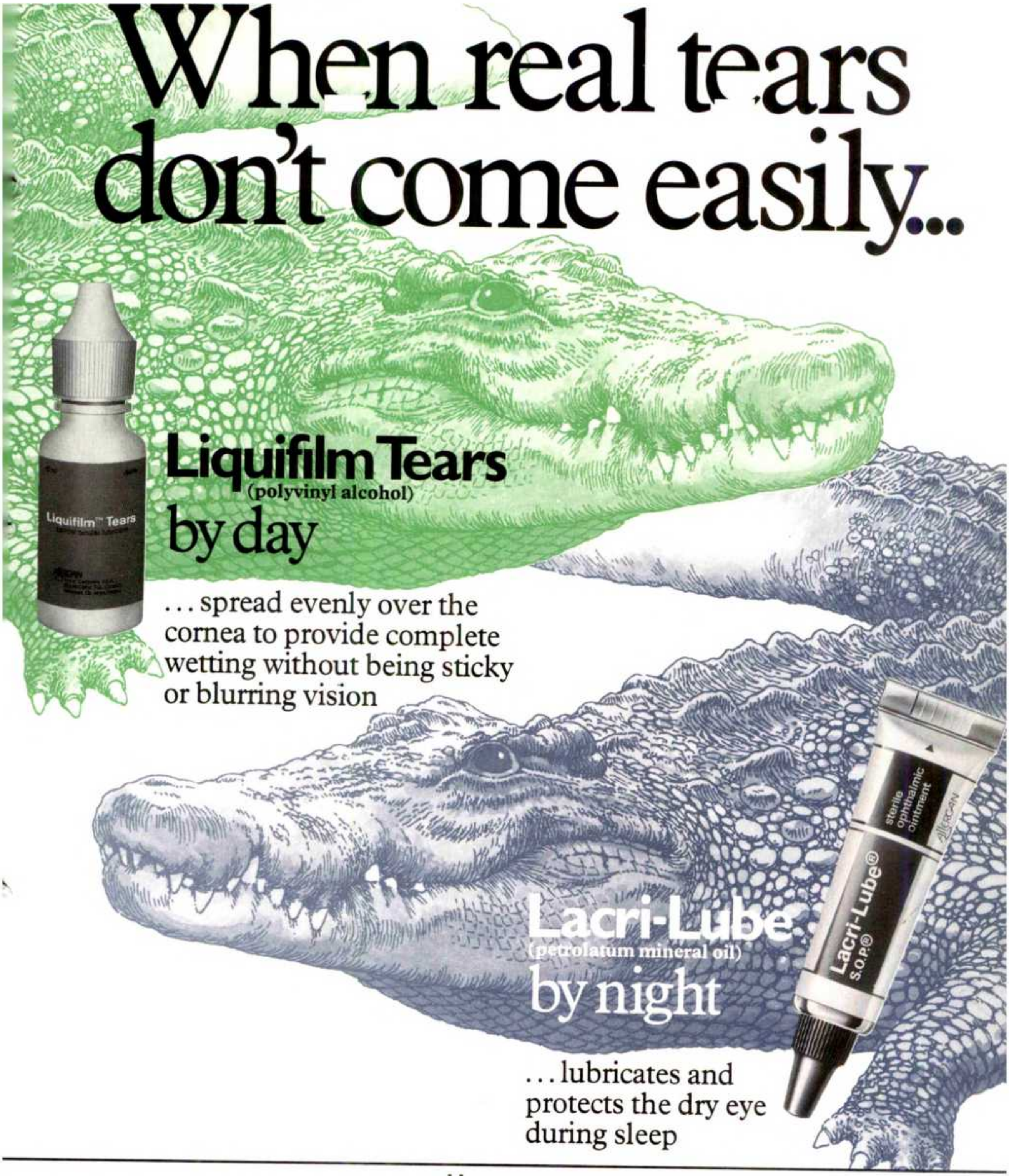
21 Yannuzzi LA, Landau AN, Turtz AI. Incidence of aphakic cystoid macular edema with the use of topical indomethacin. *Ophthalmology* 1981; **88:** 947–54.

22 Kraff MC, Sanders DR, Jampol LM, *et al.* Prophylaxis of pseudophakic cystoid macular edema with topical indomethacin. *Ophthalmology* 1982; **89:** 885–90.

23 Bito LZ, Salvador EV. Intraocular fluid dynamics. III. The site and mechanism of prostaglandin transfer across the blood intraocular fluid barriers. *Exp Eye Res* 1972; **14:** 233–41.

24 Bito LZ, DeRousseau CJ. Transport functions of the blood-retinal barrier system and the micro-environment of the retina. In: Cunha-Vaz JG, ed. *The blood-retinal barriers.* NATO Advanced Study Institutes Series. New York and London, Plenum Press, 1979; **32:** 133–63.

25 Palestine AG, Brubaker RF. Pharmacokinetics of fluorescein in the vitreous. *Invest Ophthalmol Visual Sci* 1981; **21:** 542–9.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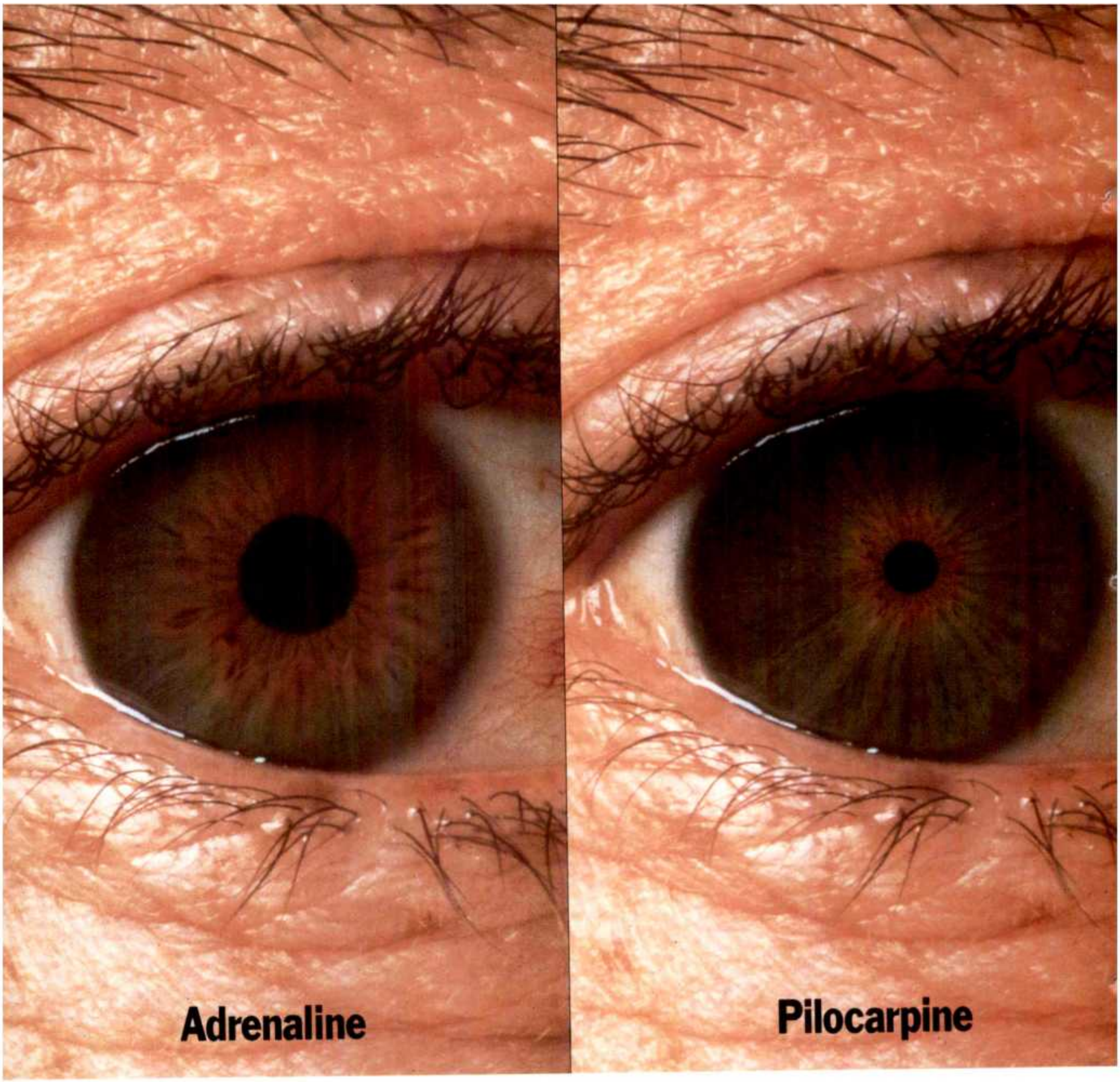

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Monitored posterior transcleral drainage of subretinal fluid

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SUMMARY A simple method for drainage of posteriorly-sequestrated subretinal fluid following vitrectomy and fluid/gas or fluid/silicone oil exchange is described. Deliberate retinotomy is thereby avoided.

After vitrectomy and membrane dissection for complicated retinal detachments surgeons are sometimes faced with the problem of achieving complete reattachment of bullously elevated retina intraoperatively in order to maximise the efficacy of postoperative internal tamponade of breaks. Internal transretinal drainage of subretinal fluid (SRF), with simultaneous exchange of vitreal fluid for air/gas mixture or silicone oil, offers a safe and simple means of achieving such 'hydraulic reattachment'[1] provided a retinal break is conveniently located posteriorly. Where the causative break is located peripherally, however, it may prove impossible to drain all SRF internally, because the buoyancy of injected gas or silicone oil compresses the anterior retina against the pigment epithelium, with 'posterior sequestration' of SRF. In anticipation of this problem, or confronted with such sequestration, standard transcleral release of SRF or deliberate posterior retinotomy followed by internal SRF drainage has been advocated.[1 2] But each method is associated with significant risks and practical difficulties. The purpose of this report is to popularise a simple, effective, and safe method of drainage of posteriorly sequestrated SRF during common gauge vitreous microsurgery.

Material and methods

Monitored posterior transcleral drainage of SRF with simultaneous intravitreal injection of gas or silicone oil is a modification of the SRF drainage techniques employed for many years by Scott in Cambridge and Wilder in Chicago. The only instrumentation required is a standard 20 gauge hypodermic needle, which offers the best compromise between minimum desirable size and necessary strength of the needle shaft. The distal 2 mm of the needle is bent with artery forceps to 100° (while the sharpness of the tip is maintained), and the shaft is also gently bent to conform with the contour of the globe (Fig. 1). Attachment of the needle to a 2 ml syringe provides a useful handle for the manipulations.

The procedure is monitored throughout by indirect ophthalmoscopy (though biomicroscopic monitoring

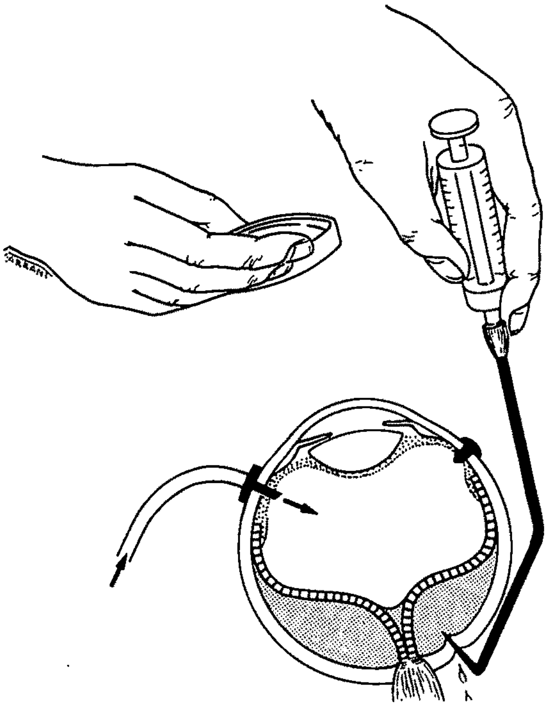

Fig. 1 *Monitored transcleral drainage of posteriorly sequestrated subretinal fluid.*

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is also possible). After three-port vitrectomy and membrane dissection, all preretinal fluid is exchanged for the gas mixture or silicone oil with a Charles flute needle or linear suction device.[1] The two active sclerotomies are then temporarily plugged. The 'ankle' of the bent needle is slid posteriorly through Tenon's space just below the medial rectus (any vortex veins being thus avoided) and the sharp tip is then directed normal to the sclera. An indentation is created and can be observed under the retina some 3 or 4 mm inferonasal to the optic disc, that is, peripheral to the site of penetration of the short posterior ciliary arteries. With the eye tension 'firmed' by gas or oil injection (so that scleral indentation and possible retinal apposition to the pigment epithelium at the sclerotomy site are minimised) the sclera is penetrated by a sharp tug on the bent needle, and 'flashing steel' is observed in the subretinal space. Myopic eyes are most readily penetrated owing to the thinness of the sclera. SRF drains round the needle, and the retina progressively flattens in a controlled fashion while intravitreal injection proceeds. Visualisation and control are easier with silicone oil than with gas. Drainage usually continues after removal of the needle tip from the subretinal space, though gentle massage of the area round the sclerotomy is occasionally required to flatten the retina completely. No retinal coagulation is used at the sclerotomy site.

Further internal drainage of preretinal fluid over the optic disc is generally necessary in order completely to fill the vitreous cavity with silicone oil. During gas exchange in phakic eyes, however, an incomplete preretinal fill is desirable in order to reduce the risk of gas induced cataract postoperatively. Nevertheless the extent of gas filling of the globe is such that no more than 20% sulphahexa fluoride gas/air mixture is used so as to preclude postoperative expansion of the gas bubble.

Results

Of the 21 operations in which posterior transcleral SRF drainage was attempted the retina completely reattached intraoperatively in all but one; the exception was a prephthisical eye with very thick sclera and choroid. The nature of the retinal detachment had no influence on the effectiveness of the procedure, whether due to diabetic combined rhegmatogenous and traction detachment, giant retinal tear, or rhegmatogenous retinal detachment with or without massive periretinal proliferation.

In only two procedures did significant subretinal bleeding result (and this mainly drained outside the eye). Retinal tearing or incarceration in the posterior sclerotomy was not seen. There were no late complications (such as fibrovascular ingrowth), and the only persistent sign of posterior drainage was a focal 0·5 mm white spot marking the defect in the pigment epithelium, Bruch's membrane, and choroid.

Discussion

At first sight posterior SRF drainage unguarded by sclerotomy sutures would appear to be a dangerous method of SRF release. This has not proved to be the case in practice. The risk of choroidal haemorrhage is reduced by the maintenance of intraocular pressure throughout the procedure, the sharp choroidal penetration (thus avoiding tractional rupture of veins), the site of drainage away from large choroidal vessels, and the absence of choroidal congestion induced by prior cryotherapy. If there is bleeding into the subretinal space, the blood tends to be evacuated along with SRF while choroidal vascular thrombosis becomes established. The risk of retinal incarceration and prolapse is reduced by the ophthalmoscopic monitoring, the controlled intravitreal injection, and the small size of the sclerotomy (which nevertheless stays open until all SRF is expressed, because the contour of the scleral envelope is maintained). In addition the retina is stretched out beneath the vitreal gas or silicone oil globule. A similar effect is utilised to 'reduce' vitreoretinal prolapse through a pars plana entry site during vitrectomy for bullous retinal detachment.[2]

Monitored posterior SRF drainage is therefore preferred over other sequential or simultaneous techniques of transcleral drainage and intravitreal injection. It obviates the need for deliberate posterior retinotomy and internal SRF drainage, with its attendant risks of bleeding, postoperative reopening of the retinotomy, and stimulation of periretinal membrane proliferation. Postoperative positioning of the patient can then be directed entirely to tamponade of the causative breaks rather than to an additional iatrogenic hole. The complete retinal reattachment facilitates cryocoagulation of breaks and localisation of episcleral buckles, minimises pigment fallout under the retina or production of folds of redundant retina, and maximises the efficacy of postoperative internal tamponade (which is especially valuable for inferiorly located breaks unsupported on a buckle).

I am grateful to Miss Heather Lucas for preparing the manuscript and Mr Terry Tarrant for the illustration.

References

1 Charles S. *Vitreous microsurgery*. Baltimore: Williams and Wilkins, 1981.
2 Michels RG *Vitreous surgery*. St Louis, Toronto, London: Mosby, 1981.

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Pathogenesis and treatment of recurrent erosion

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SUMMARY A series of recurrent corneal erosions secondary to map-dot-fingerprint dystrophy is presented. Erosions were closely related to the Hudson-Stahli line, and this may be a factor in pathogenesis. Traumatic abrasions did not demonstrate such localisation, evidence that trauma is not a primary cause. A trial of management with therapeutic contact lenses versus topical medication was performed. Therapeutic contact lenses were shown to be inferior and had a high complication rate. Recurrent erosion is often considered an indication for therapeutic contact lenses, but this is questioned and great caution recommended in such use.

This paper presents the results of a prospective study on the pathogenesis and treatment of recurrent corneal erosion secondary to map-dot-fingerprint (MDF) corneal epithelial dystrophy. Additional observations are made on the site of erosion, its relationship to the Hudson-Stahli line, and the specular microscopic appearances of the underlying endothelium. There are further observations on the relationship to trauma. The results of the first comparative trial of therapeutic contact lenses in this condition are reported.

Recurrent corneal ulceration may occur in many conditions.[1] In this paper the term recurrent erosion is confined to the epithelial loss that may occur in MDF dystrophy. This distinction is considered important, as MDF dystrophy is the commonest cause of recurrent erosion in general ophthalmic practice. The symptom complex is unlike other causes of ulceration, and the clinical and pathological findings are distinct.[2]

Recurrent erosion in MDF dystrophy may be a cause of great distress. The spontaneous attacks of severe pain, sometimes awakening the patient from sleep or on opening the eyelids, with associated epiphora, photophobia, and blurring of vision, may disrupt daily life. During an attack epithelial loss is seen with either small punctate erosions or loss of large areas of epithelium.[3] Between attacks distinctive epithelial abnormalities described as map-dot-fingerprint changes are seen on retroillumination. Fine refractile lines often in a whorl-like pattern resemble fingerprints or maps.[4] The grey or white dots are epithelial microcysts.[5] These changes may coexist and fluctuate.[6]

Possible aetiological factors are an inherited epithelial dystrophy,[7] an age-related epithelial abnormality,[8] and trauma.[9] The frequent pathological finding of epithelial oedema[10] may be secondary to endothelial dysfunction or tear film abnormality. Contact lenses have been implicated in one case.[11]

A plethora of methods to prevent erosion has been proposed. These include topical lubricating agents,[2] topical desiccating agents,[12] topical steroids,[13] debridement,[2 14] superficial keratectomy,[15] and therapeutic contact lenses.[16 17] Assessment of these treatments is difficult because there are no reports of a randomised trial or of the untreated natural history.

Patients and methods

Patients with recurrent erosion presenting to the Casualty Department at Moorfields Eye Hospital, London, between April and June 1983 were considered. The criteria for inclusion were a history of two or more previous occurrences (the patient having been seen on at least one occasion with epithelial loss), visible signs of MDF dystrophy in the same eye between episodes of erosion, no previous treatment other than topical medication, and no history of contact lens wear.

Details of age, sex, any history of trauma, and previous ocular or medical disease were recorded for each patient. The dates of the original symptoms and the number of recurrences were recorded. The symptom of pain was divided into three character-

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istics—frequency, duration, and severity—and each was graded on a scale of 1 to 4. At presentation and again when the epithelium had healed the corneal appearance was recorded on a standardised proforma. The site and size of epithelial lesions were assessed by a specially prepared scale placed over the proforma.

A random selection of 10 patients was studied by endothelial specular photomicroscopy. The site underlying the previous erosion was examined with the contact specular microscope and recorded on monochrome film. Photographs were reported on by an independent observer with no clinical knowledge of the patients.

Patients were alternately and thus randomly ascribed to one of two treatment groups. Those in the first group were given gutt. hypromellose four times a day and oculentum simplex nightly. They were reviewed at two, four, and eight weeks. Those in the second had keratometry and were fitted with a suitable radius of curvature 14 mm diameter Duragel 75 plano therapeutic contact lens. If after 1 and 24 hours the lens fit was satisfactory, they were prescribed gutt. chloramphenicol without preservative twice daily and reassessed every two weeks for eight weeks. Another lens was fitted if the original lens was seen to have a poor fit or to develop surface deposition. At eight weeks the symptoms occurring in each group were assessed for the duration of the treatment period by the above criteria. As the subjective experience of pain is so variable between patients, a control group would be unhelpful; it was decided to compare each individual patient in a longitudinal fashion before and during treatment.

A consecutive prospective series of all patients with traumatic, as opposed to dystrophic, corneal abrasion presenting to the same department in the same period were studied. The size and position of the abrasion were recorded on a similar proforma to the previously mentioned.

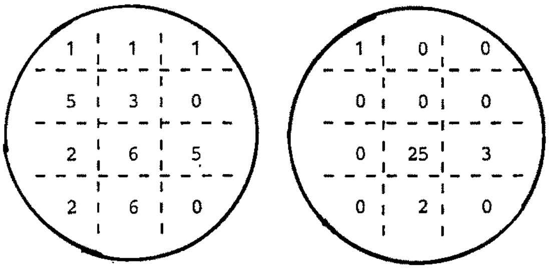

Fig. 1 *Left: traumatic abrasion. Right: recurrent erosion.*

Results

A total of 31 patients were seen; their mean age was 40 (range 20–60 years); 16 were male and 15 female. Symptoms had been occurring for an average of 14 months (range 3 months to 5 years). Twenty-one had a history of minor trauma to the affected eye. Of the total number of patients 24 were included in the trial of treatment; the others either declined to enter or failed to attend for follow-up. The general characteristics of those entering the trial are summarised in Table 1 and were seen to be similar in each group.

The position of recurrent erosions and abrasions recorded are shown in Fig. 1. A Hudson-Stahli line was found in 11 (35%) eyes with recurrent erosion, and in all these cases the recurrent erosion and Hudson-Stahli line were in the same segment. In the 20 cases in which there was no detectable Hudson-Stahli line the erosion was at the usual site of the line in 17 (85%) or in an immediately adjacent segment in two (10%) and distant in only 1 case (5%). Traumatic abrasions occurred all over the cornea and were not associated with the site of the Hudson-Stahli line.

Table 1 *General characteristics of patients entering trial*

Group	*No.*	*Age in years*		*Sex*		*Duration of symptoms in months*		*Pain*		
		Mean	*Range*	*M*	*F*	*Mean*	*Range*	*Frequency*	*Duration*	*Severity*
1	13	42	22–49	8	5	7	3–15	2	3	2·3
2	11	45	29–60	4	7	10	2–24	2·3	2·6	2·5

Table 2 *Results of treatment*

Group	*No symptoms*	*Improved on 3 scores*	*Improved on 2 scores*	*Improved on 1 score*	*Same*	*Worse on 3 scores*
1	10	1	2	0	0	0
2	3	2	2	1	1	2

Of the 10 patients who had endothelial specular photomicroscopy the appearances were normal in six; four showed essentially normal endothelium with blebbing, which was thought to be a response to the diagnostic contact lens applied.[18]

The results of treatment in the two groups are summarised in Table 2. This refers to the pain only, subdivided into its three characteristics. In group 1, treated with topical agents, no complications other than further recurrent erosions were seen. In group 2, in addition to poorer results of treatment, complications ensued in seven patients. Three had extensive epithelial loss under the contact lens similar to that occurring during recurrent erosion; in two this led to the lens being abandoned. In four patients the contact lens was frequently lost and had to be replaced many times.

Discussion

In this group of patients the usual site of recurrent erosion was seen to be very localised. Traumatic abrasions do not respect such boundaries. This fact, coupled with the frequent lack of a history of trauma, previous reports of unilateral trauma having bilateral erosion,[11] and unilateral erosions having bilateral signs,[2 4] suggests that trauma is unlikely to be the principal causative factor.

The previously unrecorded close positional association between the Hudson-Stahli line and recurrent erosion may imply either that the pathogenesis of the two is similar or that the Hudson-Stahli line is a causative factor in recurrent erosion. This may be a local epithelial abnormality. Alternatively it may be a localised expression of a generalised epithelial abnormality at this meeting point of epithelium migrating from the inferior and superior limbal palisades.

The specular appearances of the endothelium are normal. There is no morphological support for the theory that an endothelial abnormality is the underlying problem.

Medication in the treatment of group 1 was chosen as being the most innocuous of those previously suggested. The contact lens used in group 2 is one of the most frequently used at this hospital and provides a very high oxygen transmission.[19] As the average duration of symptoms is many times the duration of treatment, it is likely that the alteration noted is attributable to the therapeutic effect rather than to the usual fluctuation of the disease.

The results in accordance with previous findings show that topical medications are very effective.[2 12] Until now therapeutic contact lenses have not been formally assessed in this condition, and they are here seen to be inferior in efficacy and accompanied by a high complication rate. Two previous reports of the use of therapeutic contact lenses in recurrent ulceration from all causes, not specifically MDF dystrophy, suggest a beneficial effect in 30–50%, but neither was a formal trial.[16 17] The serious complications of therapeutic lenses such as corneal infection or vascularisation did not occur in our trial, but we have seen them in the use of therapeutic lenses for this condition. The absence of serious complications may be due to prophylactic antibiotics and close follow-up, but good fortune may have played a part. It is stressed that these complications may permanently impair vision, whereas the effect of recurrent erosion on vision is usually minimal and transient. It is suggested that the use of therapeutic contact lenses should be restricted to severely symptomatic cases in which close follow-up can be guaranteed.

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References

1 Keynon KR. Recurrent corneal erosion; pathogenesis and treatment. *Int Ophthalmol Clin* 1979; **19:** 169–93.
2 Brown NA, Bron AJ. Recurrent erosion of the cornea. *Br J Ophthalmol* 1976; **60:** 84–96.
3 Chandler PA. Recurrent erosion of the cornea. *Am J Ophthalmol* 1945; **28:** 355–67.
4 Brown NA, Bron AJ. Superficial lines and associated disorders of the cornea. *Am J Ophthalmol* 1976; **81:** 34–50.
5 Bron AJ, Tripathi, RC. Cystic disorders of the corneal epithelium. I. Clinical aspects. *Br J Ophthalmol* 1973; **57:** 361–73.
6 Laibson, RP. Microcystic corneal dystrophy. *Trans Am Ophthalmol Soc* 1976; **74:** 488–531.
7 Laibson PR, Krachmer JH. Familial occurrence of dot-map-(microcystic) fingerprint dystrophy of the cornea. *Invest Ophthalmol Visual Sci* 1975; **14:** 397–9.
8 Werblin TP, Hirst LW, Stark WJ, Maumenee IH. Prevalence of map-dot-fingerprint changes in the cornea. *Br J Ophthalmol* 1981; **65:** 401–9.
9 Rodriegues MM, Fine PS, Laibson PR, Zimmerman LE. Disorders of the corneal epithelium: a clinico-pathological study of dot geographic and fingerprint patterns. *Arch Ophthalmol* 1974; **92:** 475–82.
10 Tripathi RC, Bron AJ. Cystic disorders of the corneal epithelium: pathogenesis. *Br J Ophthalmol* 1973; **57:** 376–90.
11 Flynn MA, Easterly DB. Bilateral recurrent erosion of the cornea. *Am J Ophthalmol* 1966; **62:** 964–6.
12 Foulks GN. Treatment of recurrent corneal erosion with topical osmotic colloidal solutions. *Ophthalmology* 1981; **88:** 801–3.
13 Lowe RF. Recurrent erosion of the cornea. *Br J Ophthalmol* 1979; **54:** 805–9.
14 Trobe J, Laibson PR. Dystrophic changes in the anterior cornea. *Arch Ophthalmol* 1972; **87:** 378–82.
15 Broderick JD, Dark J, Peace GW. Fingerprint dystrophy of the cornea. *Arch Ophthalmol* 1974; **92:** 483–9.
16 Mobilia EF, Foster OD. Management of recurrent corneal erosions with ultrathin lens. *Contact Intraoc Lens Med J* 1978; **4:** 25–9.
17 Lemp P. Role of bandage lenses in recurrent erosion. *Contact Intraoc Lens Med J* 1977; **3:** 28–32.
18 Buckley RJ. Transitory endothelial changes induced by soft contact lens. In: Henkind P, ed. Acta XXIV International Congress of Ophthalmology. Philadelphia: Lippincott, 1983.
19 Woodward EJ. Therapeutic contact lenses, form and materials. *Contacto* 1979; **23:** 14–17.

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Baseball orbital implants: a review of 39 patients

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SUMMARY Thirty-five secondary and six primary 'baseball' implants—acrylic balls in envelopes of donor sclera—were followed up for a minimum of 24 months. 97·1% secondary and 50% primary implants were retained. Volume replacement was satisfactory in 83·8% with a single operation, and motility of the artificial eye was at least 14° of horizontal gaze in 86%, at least 7° of upgaze in 95%, and at least 14° of downgaze in 62·6%. Ptosis associated with the procedure occurred in 22%, and 12·2% developed a shallow fornix with instability of the artificial eye.

Removal of an eye results in a volume deficit in the orbit of about 7 ml, and the cosmetic effect of a perfectly made artificial eye may be spoiled by inadequate volume replacement. The volume of most prosthetic eyes is about 2 ml, and the simple addition of bulk to the prosthesis alone often fails to correct the enophthalmos and deep upper lid sulcus which develop invariably in adults and frequently in children. Such a bulky prosthesis cannot be supported indefinitely by the lower eyelid, which stretches, leading to the features of the 'postenucleation socket syndrome'—enophthalmos, deep upper lid sulcus, lower lid laxity, and ptosis.

These uncosmetic changes can be reversed by sharing the required volume replacement between the prosthesis and a buried orbital implant placed within the muscle cone. Such an implant should be chemically and biologically inert, easy both to insert and to cover anteriorly with conjunctiva, and designed to incorporate the eye muscles to reduce migration within the orbit and to increase motility of the prosthesis.

Since Mules first implanted glass spheres 100 years ago an impressive variety of primary and secondary implants have been designed. Because the rectus muscles may be difficult to identify, once an anophthalmic socket has healed without an implant in situ, secondary implants often have no facility for attachment of the muscles. Recent examples include glass beads,[1] expandable silicone spheres,[2] and RTV silicone.[3] The baseball implant, an acrylic ball in an envelope of donor sclera, was described by Frueh and Felker.[4] Although described as a secondary implant its design allows primary implantation as well, and it is equally effective whether or not the rectus muscles are found.

An 18 mm diameter sphere has a volume of 3·1 ml but within a scleral covering the volume is about 4 ml, which with a light prosthesis is adequate to correct most cases of postenucleation socket syndrome.

Patients and methods

Forty-three implants were placed in 41 patients between March 1979 and March 1982. All had features of the postenucleation socket syndrome due to inadequate volume replacement in the orbit.

PREPARATION OF DONOR SCLERA

A donor eye with the cornea removed is everted and the ocular contents cleared away. The scleral envelope is stored in 70% alcohol in a refrigerator. When required the sclera is washed in six changes of saline over 24 hours and placed in an antibiotic such as framycetin sulphate 15 minutes before use.

SURGICAL TECHNIQUE

Adult patients are given a 100 mg indomethacin suppository 12 hours before operation.

Secondary implantation

The fat in the muscle cone is exposed by making a horizontal conjunctival incision in the centre of the

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socket. This layer is dissected free from underlying Tenon's capsule as far as the fornices. Tenon's capsule is opened horizontally at the same level as the conjunctiva, and the intraconal fat should come into view. If an implant is found, it should be removed carefully to avoid damage to the rectus muscles and levator.

An attempt should be made to identify the rectus muscles. If found they are tagged with double armed 4 'O' chromic catgut sutures. An acrylic ball is selected which comfortably fills the space in the muscle cone. Too large an implant increases the risk of extrusion, reduces levator function, and makes the fitting of a satisfactory prosthesis difficult. Too small an implant provides inadequate volume replacement. We normally use a 16–20 mm ball. This is sewn into the envelope of donor sclera with long-acting absorbable sutures such as 6 'O' polyglycolic acid sutures.

The scleral covered ball is placed in the muscle cone, and the medial, lateral, and inferior rectus muscles are attached in their normal orientation to the surface of the implant a few millimetres short of its anterior pole. If the superior rectus is also attached a ptosis may result from traction on the levator, so it is allowed to retract. After attachment of the muscles the double-armed sutures are brought through overlying Tenon's capsule and conjunctiva and tied. They should not be tied too far into the fornices or these will be shortened. If the muscles cannot be found, the three double-armed sutures are attached to the sclera at the same three sites and brought to the surface of the conjunctiva in the same way.

Tenon's capsule and conjunctiva are closed without tension in two layers with interrupted absorbable sutures.

Primary implantation

After enucleation the hole in posterior Tenon's capsule through which the optic nerve passed is opened widely to expose orbital fat. The muscles are marked with double-armed 4 'O' chromic catgut sutures, and the operation proceeds as described above.

A clear glass or plastic shell is fitted to maintain the fornices, and we normally prescribe indomethacin 25 mg tds for five days and topical chloramphenicol for two weeks postoperatively. The patient may be fitted with a temporary artificial eye in about six weeks and referred for impression fitting of the final prosthesis in three to six months.

Of the 43 implants in the series 24 were re-examined and 15 patients had their hospital records reviewed. Two patients had inadequate detail in their records and could not be traced for examination so were not included. A total of 35 secondary and six primary implants were reviewed in 39 patients. Attention was directed to retention of the implant, volume correction, motility of the prosthesis, and complications of the technique.

Results

RETENTION OF THE IMPLANT

Thirty-four of the 35 secondary implants (97·1%) were retained for 24–60 months' follow-up (average 40 months), and three of the six primary implants (50%) were retained for 36–53 months' follow-up (average 44·7 months).

Table 1 *Retained implants*

Months of follow-up	*Primary*	*Secondary*
24–35	—	13
36–47	2	11
48–60	1	10
Total	3	34

The secondary implant which extruded was a 20 mm ball which became exposed at three days and was removed at 14 days. It had been used to replace a small Castroviejo implant removed at the same operation. The three primary implants were extruded at 8, 14, and 21 days respectively. All followed enucleation for recent trauma. Two were replaced with secondary baseball implants at six months and seven months respectively, and these have each been retained for 27 months to date. The retained primary implants followed enucleations for a painful blind eye (two cases) and choroidal malignant melanoma (one case).

In two secondary implants exposure occurred, but the implant was retained following resuture of the conjunctiva. One was a 20 mm ball, and resuture at 17 days was sufficient. The other was an 18 mm ball and required resuture at one month. Eighteen months later the implant became re-exposed, and a scleral patch was used to reinforce Tenon's capsule anteriorly. No further exposure has occurred after 17 months' follow-up.

VOLUME CORRECTION

If the extruded implants are omitted, 23 of the remaining 37 implants achieved full volume correction with a single operation. Fourteen patients (37·8%) had residual enophthalmos or upper lid sulcus, but in only six (16·2%) was it necessary to supplement the volume with an orbital floor implant. Thirty-one (83·8%) had a satisfactory result with a single operation.

MOTILITY OF THE PROSTHESIS

A sample of 22 patients were re-examined specifically for motility of the artificial eye. Movement of the limbus was measured for horizontal gaze, upgaze, and downgaze.

Table 2 *Motility of prosthesis*

Limbal movement mm	*Horizontal*	*Upgaze*	*Downgaze*	*Total*
<1	—	1	1	2
1	3	8	7	18
2	7	7	4	18
3	5	5	9	19
>3	7	1	1	9

With approximately 7° being allowed for each millimetre, 86% achieved at least 14° horizontal movement, 95% had at least 7° upgaze, and 63·6% had at least 14° downgaze.

COMPLICATIONS

Ptosis. Although it was not always recorded in the hospital notes we assume that almost all patients in the series had at least a minimal ptosis preoperatively as a feature of the postenucleation socket syndrome. In seven patients (17·1%) the preoperative ptosis was not corrected by orbital implantation and prosthetic adjustment alone. Six (85·7%) of these required ptosis surgery.

Table 3 *Analysis of patients with ptosis*

	Total	*Ptosis surgery*
Ptosis corrected by implant alone	?25	—
Marked ptosis before and after implant	7	6
Marked ptosis after implant only	0	6
Total	41	12 (29·3%)

Nine patients (22%) developed more marked ptosis after baseball implantation, and six (66·7%) of these required surgical correction. All patients with ptosis had at least 5 mm of levator function. Three had a posterior levator resection, eight had an anterior levator resection, one had a Fasanella-Servat operation. There was no correlation between the severity of the ptosis and the age of the patient, the age at enucleation, the reason for enucleation, or the size of the implant.

Shallow fornices. Five patients (12·2%) with normal fornices before implantation developed a shallow fornix postoperatively. Of these only two (40%) required subsequent fornix reconstruction with oral mucosa. Seven patients (17%) had been noted to have shallow fornices before implantation, and these were usually worse postoperatively. Five of this group (71·4%) required fornic reconstruction. Of the 12 patients with a shallow fornix after implantation the lower fornix alone was shallow in eight, the upper fornix alone in one, and both fornices in three.

Other complications. One implant, inserted into a grossly traumatised socket, migrated inferiorly and was removed electively at 34 months. A new baseball implant was placed at a higher level at the same operation and has been retained without incident for 11 months so far. Three patients developed conjunctival implantation cysts—two in the centre of the socket and one in the upper fornix. All were removed easily with direct closure of the conjunctiva.

Discussion

Apart from the minor inconvenience of preparing donor sclera the baseball implant is easy to prepare and insert. A moderate amount of postoperative oedema is common, as with all implants, and is reduced by indomethacin.

Selection of the correct size of acrylic ball is important. Too large an implant results in a shallow socket, poor fornices, and an increased risk of extrusion. Ocular prostheses should be at least 4 mm thick to achieve a realistic appearance, and this may not be possible if the convex posterior wall of the socket extends too far forward. A proptotic artificial eye may hinder lid closure, causing upper lid retraction, or the large implant may limit movement of the levator, causing ptosis. Too small an implant will not correct enophthalmos and a deep sulcus in the upper lid.

Extrusion is usually associated with oedema, haemorrhage, infection, or poor surgical technique and occurs most commonly within six months of surgery. The extruded primary implants in our series followed recent trauma and were probably due to oedema. We now avoid the baseball implant after enucleation for recent trauma. The single secondary implant which extruded was inserted at the time of removal of another implant. The 20 mm ball used may have been too large for the socket, or the trauma of removing the primary implant may have caused added oedema. Retention of the baseball implant is comparable with that of other buried implants, all of which have an extrusion rate of less than 4%.[5-8] Implanted sclera remains grossly unchanged for several years[9] and provides a stable pocket for the acrylic ball. There is some histological evidence that sclera gradually dissolves,[9] but by then the pseudocapsule of adjacent tissues in the orbit provides adequate support.

If exposure of an implant occurs, resuture of the conjunctiva alone is often inadequate, though it was initially successful in our two cases. The use of a scleral patch[10] extending almost to the fornices between Tenon's capsule and the conjunctiva is a better alternative and was successful when re-exposure occurred after 18 months in the second case.

Volume correction is excellent and lasting with the baseball implant and allows a light artificial eye to be fitted, which gains added support from the convex surface of the implant. When volume replacement was inadequate, it was noted as soon as postoperative oedema had settled. We have not observed significant late volume deficiency—for example, due to massive fat atrophy. Despite this some fat atrophy probably occurs, as with any socket surgery, and careful dissection should reduce this to a minimum. Significant undercorrection is best managed with a supplementary implant—usually a silicone block cut to size—introduced subperiosteally along the floor of the orbit via an incision in the lower lid.

Despite the apparent disadvantage of a 'ball and socket' joint between prosthesis and implant, motility was acceptable and comparable with that of the quasi-integrated implants.[6] The good motility is probably due to movement of the fornices, well preserved because of the sutures between the muscles, implant, and conjunctiva.

Mild ptosis following enucleation is often corrected once the fulcrum over which the levator acts is raised by insertion of an implant. Inadequate size of implant fails to achieve this. Some ptoses do not improve and a few are made worse, probably owing to operative trauma to the levator and postoperative oedema. Postoperative ptosis may be improved by building up the prosthesis either on its anterior surface or upper rim. The failures are treated surgically. Levator resection is suitable for any ptosis with a levator function of more than 4 mm. Less levator function that this should be treated with a brow suspension. Ptosis of 2 mm or less with a levator function of more than 12 mm can be treated with a Fasanella-Servat operation.

Shortened conjunctival fornices in a vertical direction may occur after enucleation unless care is taken with preservation and closure of conjunctiva. Insertion of an implant may exacerbate already shortened fornices, especially if it is too large. Closure of Tenon's capsule over a baseball implant may cause shortening of the fornices unless care is taken to dissect conjunctiva from Tenon's capsule as far as the fornices. Redundant conjunctiva in the centre of the socket is then avoided, and the fornices maintain their maximum possible depth. Despite this we usually avoid use of a baseball implant if the fornices are found to be short preoperatively. A dermofat graft[11] is a satisfactory alternative, though it tends to lose bulk during the first six months when used as a secondary implant.[12] Conjunctiva grows over the anterior surface of a dermofat graft within six weeks. The same may occur if conjunctiva is recessed from the anterior pole of a scleral patch placed in front of a buried orbital implant,[9] leaving more conjunctiva in the fornices. We have no experience of this and prefer to reconstruct a doubtful fornix with oral mucosa at the time of insertion of the implant if a baseball is to be used.

Implants that migrate usually do so in a downward and lateral direction, causing ectropion and loss of the lower fornix, with failure to retain the prosthesis. Minor degrees of migration may occasionally be managed with modification of the prosthesis, but often removal of the implant and insertion of a secondary implant is essential. The single case of migration in our series occurred in a grossly scarred socket.

The occurrence of conjunctival implantation cysts is well documented after enucleation surgery.[13] They may occur within the orbit close to the implant or on the surface as in our series. They usually cause discomfort as they enlarge and may make wearing of the prosthesis impossible. Cysts close to the conjunctival surface are usually easy to remove. If there is doubt about the strength of the remaining layers anterior to the implant, the area should be reinforced with a patch of donor sclera between conjunctiva and Tenon's capsule.

CONCLUSION

The baseball implant can be recommended as a safe and convenient secondary implant and as the first approach to a volume deficit in the anophthalmic socket. It should probably be avoided if the conjunctival fornices are already shallow as a result of enucleation or other socket surgery.

This series of primary baseball implants is too small to allow us to draw valid conclusions. We now avoid this implant after recent trauma, but it may well prove to be of value in other cases.

References

1 Smith B, Obear M, Leone CR. The correction of enophthalmos associated with anophthalmos by glass bead implantation. *Am J Ophthalmol* 1967; **64:** 1088–93.

2 Soll DB. Insertion of secondary orbital implant. *Arch Ophthalmol* 1973; **89:** 214–6.

3 Vistnes LM, Paris GL. Uses of RTV silicone in orbital reconstruction. *Am J Ophthalmol* 1977; **83:** 577–81.

4 Frueh BR, Felker GV. Baseball implant – a method of secondary insertion of an intraorbital implant. *Arch Ophthalmol* 1976; **94:** 429–30.

5 Allen JH, Allen L. A buried muscle cone implant. *Arch Ophthalmol* 1950; **43:** 879–90.

6 Spivy BE, Allen L, Burns CA. The Iowa enucleation implant. *Am J Ophthalmol* 1969; **67:** 171–88.

7 Soll DB. Enucleation surgery – a new technique. *Arch Ophthalmol* 1972; **87:** 197–7.

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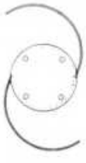

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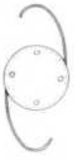

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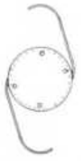

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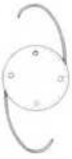

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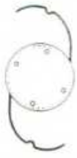

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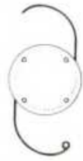

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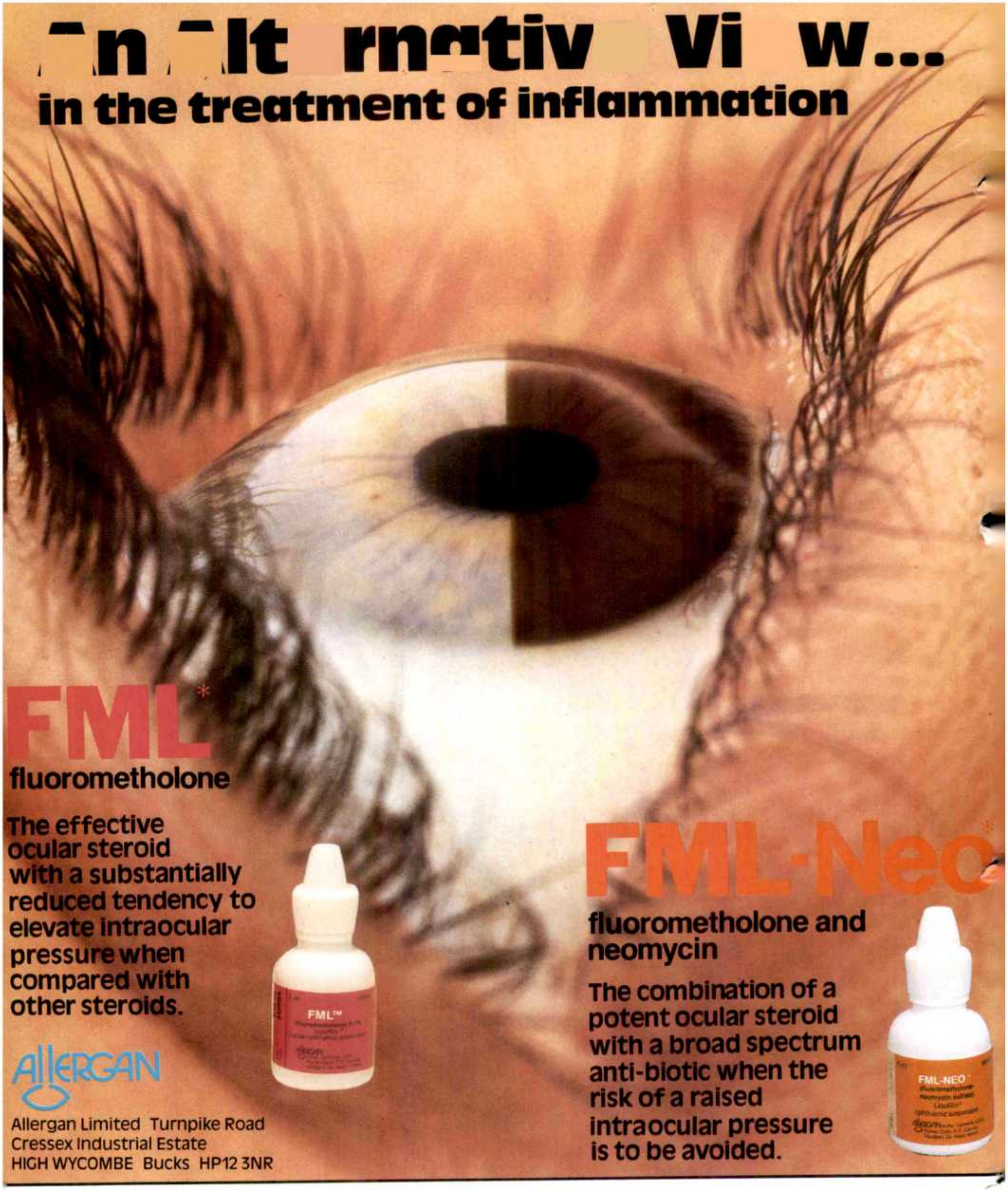

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British Journal of Ophthalmology, 1985, **69**, 443–445

Frontalis sling: a modified simple technique

S M BETHARIA

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SUMMARY A modified simple technique of brow suspension by using 4-0 Supramid (non-absorbable thread) suture and only one skin incision is described in 25 eyes of 15 cases of ptosis, including cases of congenital and mechanical ptosis and ptosis with Marcus Gunn phenomenon. This technique avoids the use of any special instruments such as the Reese ptosis knife and Wright needle.

A sling operation is by far the easiest of all ptosis operations to perform. Though it may have important disadvantages, such as the risk of lagophthalmos and lid lag in down gaze, it is the operation of choice for certain cases of gross bilateral ptosis with poor levator function as seen in the blepharophimosis syndrome, cases of mechanical ptosis, and in severe unilateral ptosis covering the pupillary area to prevent amblyopia before a definitive levator operation can be carried out.

Various kinds of material have been used for sling surgery, including skin muscle flaps, non-absorbable sutures, preserved sclera, reconstituted collagen, Silastic bands, and fascia lata. Bodian[1] used strips of human sclera successfully, whereas Iliff[2] advocated the use of reconstituted collagen. Helveston and Wilson[3] used strips of sclera woven with 4-0 Supramid for passing the sling. Tillet and Tillet[4] used a silicone sling, and Callahan[5] used a Silastic band for frontalis suspension. Crawford[6] and Fox[7] advocated the use of fascia lata.

Methods of passing the sling have been described.[6-8] The slings were rhomboidal or pentagonal in shape, and multiple incisions were made during the operation. Most of these methods are tedious and require special instruments such as a fascia lata stripper, a Wright needle, and a Reese ptosis knife for the operation, and they leave ugly scars.

Materials and methods

A modified simple technique of brow suspension is described below which has been carried out successfully on 25 eyes in 15 cases of blepharophimosis with gross ptosis, mechanical ptosis, and ptosis associated with the Marcus Gunn phenomenon after disinsertion of levator muscle from the tarsal plate (Table 1).

Table 1 *Distribution of cases*

Diagnosis	*No. of cases*	*Operation done*
Blepharophimosis syndrome	10	Bilateral sling
Congenital ptosis with Marcus Gunn phenomenon	2	Unilateral sling after disinsertion of the laevator
Mechanical ptosis (haemangioma and neurofibroma)	3	Unilateral sling

SURGICAL PROCEDURE

The operation is carried out under general anaesthesia. The first step is to lift the lid with the help of the index finger just medial to the centre of the upper lid and observe the contour of the lid margin in relation to the limbus. This gives an approximate idea of the place from which the needle has to be passed. A 5 mm wide bite is taken about 4 mm away from the lid margin by using a 15 mm curved cutting needle carrying 4-0 Supramid suture. This bite is taken through the orbicularis and the pretarsal tissue (Fig. 1). The needle is taken out and re-entered through the same point from which it has emerged and carried upwards through the plane between the orbicularis and the levator and through the single incision made above the brow (Figs. 2, 3). The other arm of the suture is similarly carried through by using a similar needle which enters through the initial opening made by the needle and is then brought out through the incision above the brow (Figs. 4, 5). A single knot is first tied, the lid is lifted, and the contour of the lid margin in relation to the limbus is observed. The tension on the two arms of the

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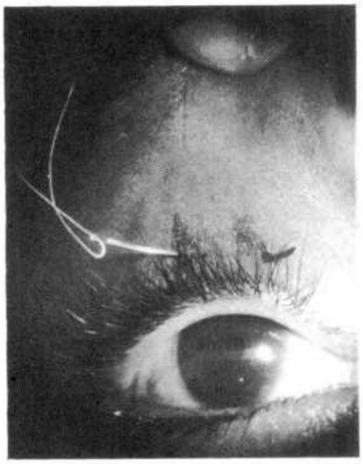
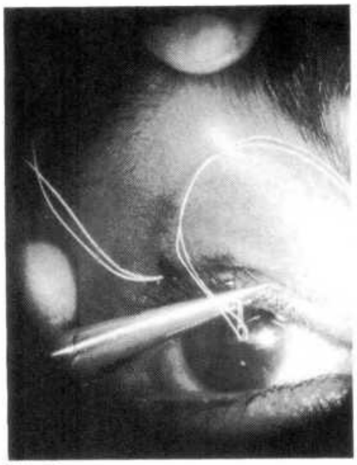


Fig. 1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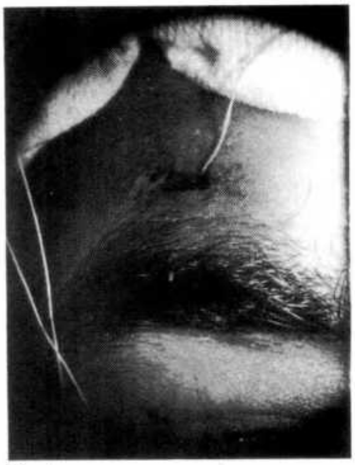
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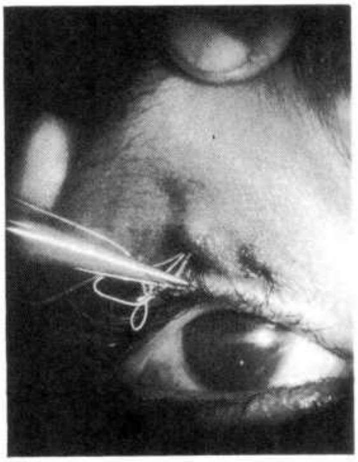
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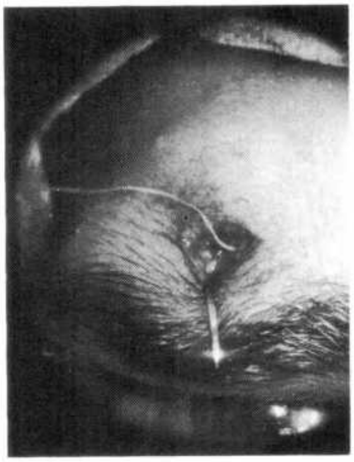
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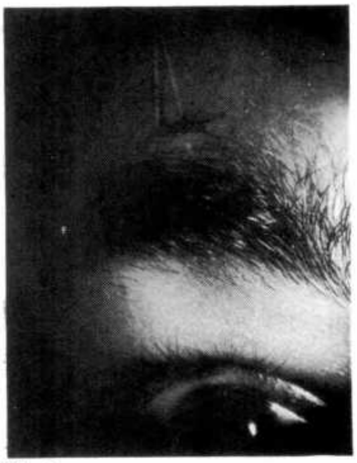
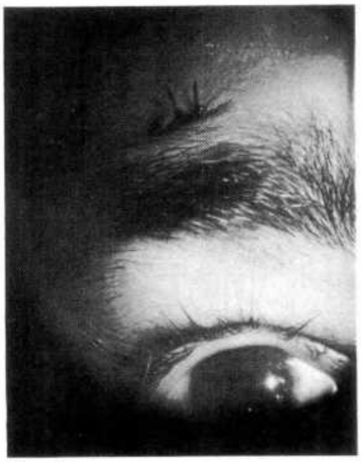


Fig. 6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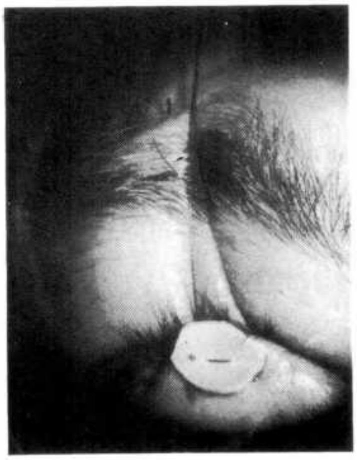
Fig. 8

Figs. 1 to 8 *Steps of the modified frontalis sling operation.*

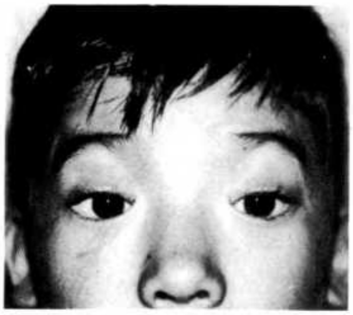

Fig. 9 *Preoperative photograph of a case of blepharophimosis syndrome. Note the arching of brows and wrinkles on the forehead suggesting frontalis overaction.*

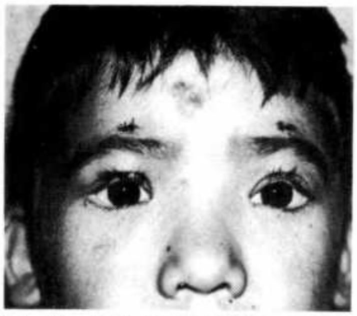

Fig. 10 *Early postoperative photograph showing a good symmetrical correction with good lid fold.*

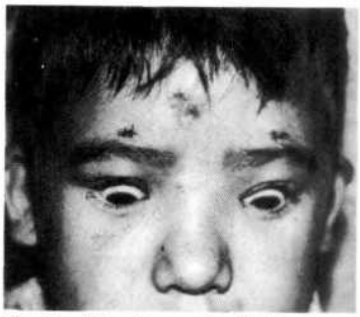

Fig. 11 *Showing marked lid lag in early postoperative period.*

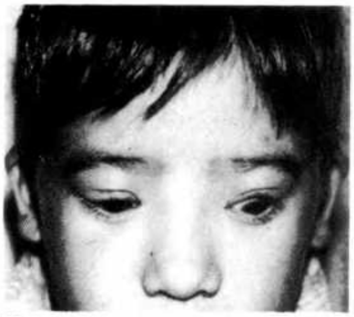

Fig. 12 *Showing reduction in the lid lag after three months.*

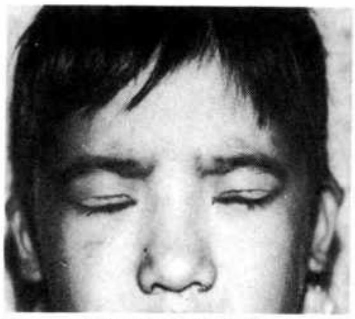

Fig. 13 *Showing very minimal lagophthalmos after the modified sling operation.*

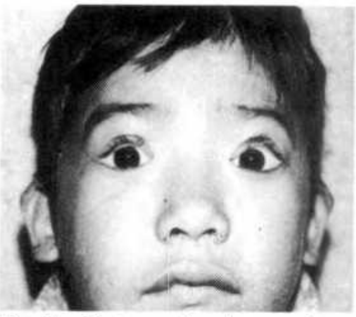

Fig. 14 *Postoperative photograph after three months showing good correction in primary gaze.*

suture is so adjusted that there is no central notching or ectropion (Fig. 6). Three square knots are tied, and the skin incision is closed with 5-0 black silk (Fig. 7). A modified Frost suture is finally made (Fig. 8).

Results and discussion

Of 15 cases operated upon so far by this technique only one had suture granuloma and infection. The lid lag, which was quite marked at the beginning, was much reduced after three months. The lagophthalmos was minimal. A good symmetrical lift with a good lid fold was obtained (Figs. 9 to 14). All the cases were followed up postoperatively for three to nine months, average six months.

This method employs only one skin incision as against six in Crawford's technique[6] of double rhomboids and five in Fox's method,[7] thereby reducing the possibility of scar marks. The central 5 mm bite through the orbicularis and pretarsal tissue eliminates the central notching, while the peripheral parts of the lid on the medial and lateral sides are lifted properly, and the contour of the lid can be correctly adjusted by pulling on the two arms of the suture. A good lid fold and symmetry were achieved by this technique. The lid lag, which was marked in the initial postoperative period, was reduced to a minimum, and there was minimal lagophthalmos. This method is extremely simple and required no special instruments.

References

1 Bodian M. Repair of ptosis using human sclera. *Am J Ophthalmol* 1968; **65:** 352–8.

2 Iliff CE. *Surgical management of ptosis*. Somerville, NJ: Ethicon, 1963: 9–12.

3 Helveston EM, Wilson DL. A suture reinforced scleral sling. *Arch Ophthalmol* 1975; **93:** 643–5.

4 Tillet CW, Tillet GM. Silicone sling in correction of ptosis. *Am J Ophthalmol* 1963; **62:** 521–3.

5 Callahan A. Correction of unilateral blepharoptosis with bilateral eyelid suspension. *Am J. Ophthalmol* 1972; **74:** 321–6.

6 Crawford JS. Repair of ptosis using frontalis muscle and fascia lata. *Trans Am Acad Ophthalmol Otolaryngol* 1956; **60:** 672–8.

7 Fox SA. Complications of frontalis sling surgery. *Am J Ophthalmol* 1967; **63:** 758–62.

8 Friedenwald JS, Guyton JS. A simple ptosis operation: utilization of the frontalis by means of a simple rhomboid shaped suture. *Am J Ophthalmol* 1948; **31:** 411–4.

British Journal of Ophthalmology, 1985, **69**, 446–448

Circulating antibodies to corneal epithelium in patients with uveitis

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SUMMARY We investigated the incidence of circulating corneal epithelium antibodies in patients with uveitis. A high percentage of the patients (42%) were positive, whereas only 4% of controls had these antibodies in their serum. Significantly more patients with anterior and diffuse uveitis had corneal epithelium antibodies than did those with posterior uveitis. Subdivision of anterior uveitis into HLA-B27 positive versus negative patients showed a higher incidence of the antibodies in the HLA-B27 positive group. A previous history of uveitis may play a role in the pathogenesis of peripheral corneal thinning diseases, for which an autoimmune aetiology has been suggested.

The peripheral corneal thinning syndrome includes many corneal ulcerative diseases such as Mooren's ulcer, Wegener's granulomatosis, polyarteritis nodosa, Terrien's disease, and rheumatoid arthritis. Many possible causes for this syndrome have been proposed, but as yet none have been proved. A recent study[1] showed that circulating immune complexes may play a role in the pathogenesis of Mooren's ulcer and marginal ulceration in the presence of collagen vascular disease. However, earlier studies suggested a humoral autoimmune response against corneal antigens as a pathogenetic mechanism of the Mooren's ulcer.[2-4] In 1969 Schaap *et al.*[2] were the first to show the presence of circulating antibodies to corneal epithelium in a patient with Mooren's ulcer. This finding was confirmed by Brown and Mondino[3,4] and other workers.[5,6] In a recent study from our institute Van der Gaag *et al.*[7] found a high incidence of circulating corneal epithelium antibodies (81%) in African patients with a Mooren's ulcer. A local control group, however, also had a high prevalence (87%) of these antibodies.

These findings raised the question whether the presence of circulating antibodies to corneal epithelium is the primary cause of the ulceration or whether these antibodies reflect a secondary phenomenon following a generalised parasitic or viral infection.[8] Another hypothesis may be that these antibodies are elicited by previous ocular inflammation. Evidence for the latter theory was obtained in the investigation reported here, studying the incidence of circulating corneal epithelium antibodies in uveitis patients. Our study shows that approximately 40% of the patients with uveitis have circulating corneal epithelium antibodies compared with 4% in a control group.

Materials and methods

Sera were obtained during an attack of uveitis from 133 patients visiting the university eye clinics of Rotterdam (Dr Baarsma), the Amsterdam Academic Hospital of the Free University (Dr Tjoa), and the Academic Medical Centre (Dr Rothova), and from 70 control persons attending the outpatient department for refraction only and staff members. All controls were questioned about previous ocular inflammation and examined with the slit-lamp for corneal defects. Patients and controls were comparable as to age and sex (patients 68 males, 65 females, average age 35 years; control group 23 males, 29 females, average age 33 years).

The uveitis patients were classified as having anterior (n=84), posterior (n=33), or diffuse uveitis (n=16). Most patients underwent routine blood screening (erythrocyte sedimentation rate, haemoglobin level, white blood cell count). We also tested immunoglobulin levels (IgG, IgM, IgA, IgE, and IgD), complement levels (C3, C4, Clq, CH50),

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circulating immune complex levels, autoantibodies (rheumatoid factor, anti-DNA, antinuclear antibody, anti-smooth muscle, anti-parietal cells, anti-mitochondria), syphilis serology, toxoplasma serology, serum angiotensin-converting enzyme and lysozyme levels, and carried out HLA-B27 typing; in the case of patients with birdshot retinopathy HLA-A29 typing was performed. Most of the HLA-B27 positive patients with anterior uveitis were examined by a rheumatologist for ankylosing spondylitis.

Circulating antibodies against corneal epithelium were assayed by an indirect immunofluorescence technique on rabbit corneas. The corneas were frozen in liquid nitrogen and 4 μm sections were cut in a cryostat. The sections were air dried on slides, overlaid with a 1/10 serum dilution in phosphate buffered saline (PBS), and incubated for 30 minutes at room temperature. The slides were subsequently washed with PBS at 37°C and incubated for 30 minutes in the dark at room temperature, with a fluorescein labelled goat anti-human immunoglobulin (Nordic) diluted 1/40 in PBS.

The slides were washed thoroughly and covered with a solution of 90% glycerin and 10% PBS containing 100 mg P-phenylenediamine to prevent fluorescence fading.[9] They were scored double blind (that is, by two separate investigators unaware of the patient's serum used) with a fluorescence microscope equipped with epi-illumination. Statistical analysis of the data was performed by the χ^2 test.

Results

Circulating corneal epithelium antibodies were found in a high percentage (42%) of the uveitis patients, whereas these antibodies occurred in only 4% of the control series (p<0·005). Two out of 52 control persons had circulating corneal epithelium antibodies (Table 1). One wore contact lenses; the other had a nebula corneae in one eye and a previous history of a foreign body in the same eye.

In the immunofluorescence technique rabbit corneas were used as a substrate. Extensive studies comparing human corneas (blood group O) with rabbit corneas as a substrate showed no differences in the results (Table 2). Incubation of positive sera with rabbit erythrocytes and lymphocytes did not show any absorbtion of the circulating corneal epithelium antibodies. These sera, positive for corneal epithelium, were specific for the cornea and did not react with other tissues, such as conjunctival epithelium, lens epithelium, oesophagus epithelium, or mucosa of the cavia lip. Only one serum reacted weakly with smooth muscle, whereas none reacted with parietal cells and thyroid.

Subdivision of the anterior uveitis group into HLA-B27 positive and negative showed that the incidence of corneal epithelium antibodies was significantly (p<0·02) higher in the HLA-B27 positive group. The presence or absence of ankylosing spondylitis in the HLA-B27 positive patients did not correlate with the presence of corneal epithelium antibodies. The patients with anterior and diffuse uveitis had a higher incidence of corneal epithelium antibodies than did those with posterior uveitis (p<0·005). No correlation was found between the presence of corneal epithelium antibodies and other immunological parameters studied, such as immunoglobulin levels, complement levels, circulating immune complexes, and other autoantibodies tested.

Table 1 *Antibodies to corneal epithelium in uveitis patients and controls*

Group	*Number of patients*	*% Positive for corneal epithelium antibodies*
Anterior uveitis		
HLA-B27 positive	35	54
HLA-B27 negative	49	30
Total	84	42
Posterior uveitis		
Behçet's disease	3	30
Toxoplasmosis	6	17
Sarcoidosis	1	0
Birdshot retinopathy	3	0
Multiple sclerosis	1	0
Pars planitis	1	0
Tuberculosis	2	50
Unknown aetiology	16	44
Total	33	30
Diffuse uveitis		
Sarcoidosis	4	75
Syphilitic infection	2	100
Behçet's disease	1	100
Ankylosing spondylitis	2	0
Unknown	7	57
Total	16	69
All uveitis patients	133	42
Control population	52	4

Table 2 *Comparison of rabbit cornea and human cornea (blood group O) used as a substrate to determine corneal epithelium antibodies*

	Rabbit cornea	*Human cornea*
Positive sera		
1	+	+
2	+	+
3	++	++
4	+	+
5	+	(+)
Negative sera		
1	–	–
2	–	–

++=Strong positive.
+=Positive.
(+)=Weak positive.

No influence was found of sex and age on the occurrence of corneal epithelium antibodies.

Discussion

Our results show a high occurrence of corneal epithelium antibodies in uveitis patients (42%) as compared with a control group (4%). Cell mediated immune reactions against corneal antigens have been described earlier in uveitis patients.[10 11] One study[11] reported that no antibodies could be found against corneal antigens by the Ouchterlony immunodiffusion technique. The immunofluorescence technique used in our study is, however, known to be more sensitive.

The pathogenesis of the peripheral corneal thinning diseases remains speculative. An immune complex mediated disease has been implicated in Wegener's granulomatosis, polyarteritis nodosa, and rheumatoid arthritis.[1 12 13]

The aetiology of Mooren's ulcer and Terrien's disease is undetermined, though an autoimmune mechanism has been proposed. Several investigators have demonstrated the presence of circulating antibodies in these patients.[2-6] In addition both immunoglobulin and complement deposits have been demonstrated in conjunctivae and corneal biopsies.[3 4]

A recent study[7] showed a high frequency of corneal epithelium antibodies (81% positive) in African patients with Mooren's ulcer. The same frequency (87%) was also found in local controls. The frequent occurrence of both Mooren's ulcer and circulating corneal epithelium antibodies in Africans compared with the rarity of Mooren's ulcer and the low incidence of corneal epithelium antibodies in Europeans would indirectly suggest that these autoantibodies have a part in the pathogenesis of the disease.

A history of a previous uveitis is present in a number of peripheral thinning diseases.[14] Corneal disorders are frequently seen in association with iridocyclitis. Some of these entities are probably caused by a viral infection of both the cornea and the uvea. On the other hand it may be that autoimmunity against the cornea is developed during the uveitis, leading to a keratouveitis. Investigation of selected patients with keratouveitis may clarify this issue.

The increased congestion and permeability of the vessels in the anterior segment may be an important prerequisite for the induction of corneal epithelium antibodies. In the case of a diffuse uveitis and anterior uveitis vascular permeability is increased, leading to a greater accessibility of the corneal epithelium antigens to the immune system, which may result in the active production of antibodies to these antigens. If these circulating corneal epithelium antibodies gain access to the corneal epithelium as a result of corneal inflammation or trauma, immune complexes are formed locally. These complexes may activate the complement system, promoting chemotaxis of inflammatory cells, finally resulting in serious damage to the corneal tissue.

We are now investigating the role of circulating corneal epithelium antibodies in the pathogenesis of corneal thinning diseases using an animal model.

References

1 Berkowitz PJ, Arentsen JJ, Felberg NT, Laibson PR. Presence of circulating immune complexes in patients with peripheral corneal disease. *Arch Ophthalmol* 1983; **101:** 242–6.

2 Schaap OL, Feltkamp TEW, Breebaart AC. Circulating antibodies to corneal tissue in a patient suffering from Mooren's ulcer (ulcus rodens corneae). *Clin Exp Immunol* 1965; **5:** 365–70.

3 Mondino BJ, Brown SI, Rabin BS. Autoimmune phenomena of the external eye. *Ophthalmology* 1978; **85:** 801–17.

4 Brown SI, Mondino BJ, Rabin BS. Autoimmune phenomenon in Mooren's ulcer. *Am J Ophthalmol* 1976; **82:** 835–40.

5 Pau H, Smitt-Graft A. Das Ulcus Rodens Mooren als mögliche autoaggressions Krankheit. *Klin Monatsbl Augenheilkd* 1983; **183:** 192–4.

6 Murray PI, Rahi AHS. Pathogenesis of Mooren's ulcer: some new concepts. *Br J Ophthalmol* 1984; **68:** 182–7.

7 Gaag R van der, Abdillahi A, Stilma JS, Vetter JCM. Circulating antibodies against corneal epithelium and hookworm in patients with Mooren's ulcer from Sierra Leone. *Br J Ophthalmol* 1983; **67:** 623–8.

8 Haspel MV, Onodera T, Prabhaka BS, Horita M, Suzuki H, Notkins AL. Virus-induced auto-immunity: monoclonal antibodies that react with endocrine tissues. *Science* 1983; **220:** 304–6.

9 Johnson GD, Gloria M, Arajo CN. A simple method of reducing the fading of immunofluorescence during microscopy. *J Immunol Methods* 1981; **43:** 349–50.

10 Feinberg BE, Shore B, Leopold IH, Henley WL. Cellular immunity in chronic ophthalmic disorders. *Am J Ophthalmol* 1972; **73:** 68–73.

11 Basu PK, McCulloch C. The presence of cell mediated immunity in uveitis. *Can J Ophthalmol* 1977; **12:** 133–9.

12 Smolin G, O'Connor GR. Introduction to immunology: special ocular considerations. In: Smolin G, O'Connor GR, eds. *Ocular immunology*. Philadelphia: Lea and Febiger, 1981: 59–68.

13 Rahi AHS, Garner A. *Immunopathology of the eye.* Oxford: Blackwell, 1976: 131.

14 Smolin G, Thoft RA. The cornea, scientific foundations and clinical practice. In: Smolin G, Thoft RA, eds. Boston, Toronto: Little, Brown, 1983: 231–92.

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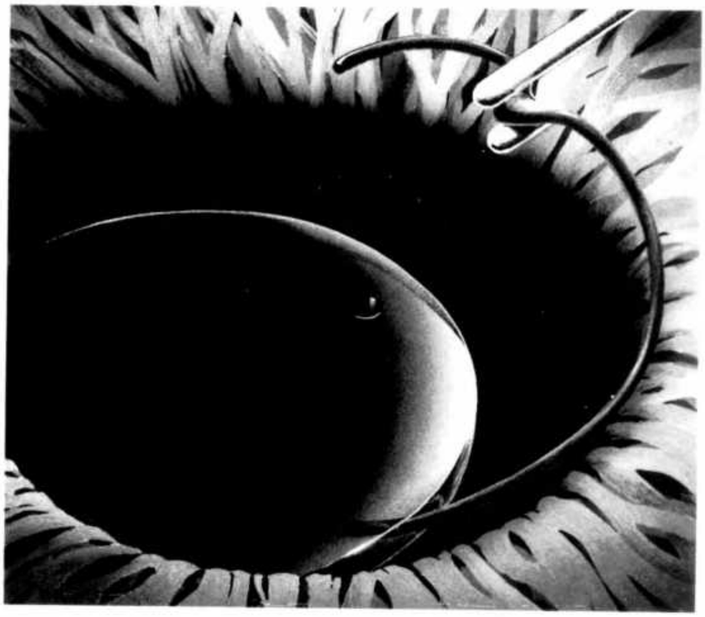

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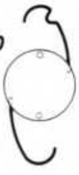

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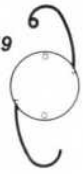

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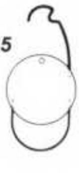

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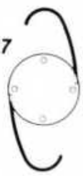

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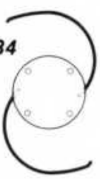

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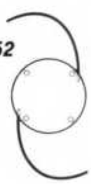

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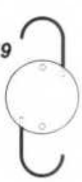

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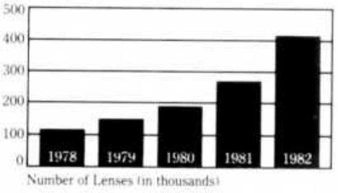

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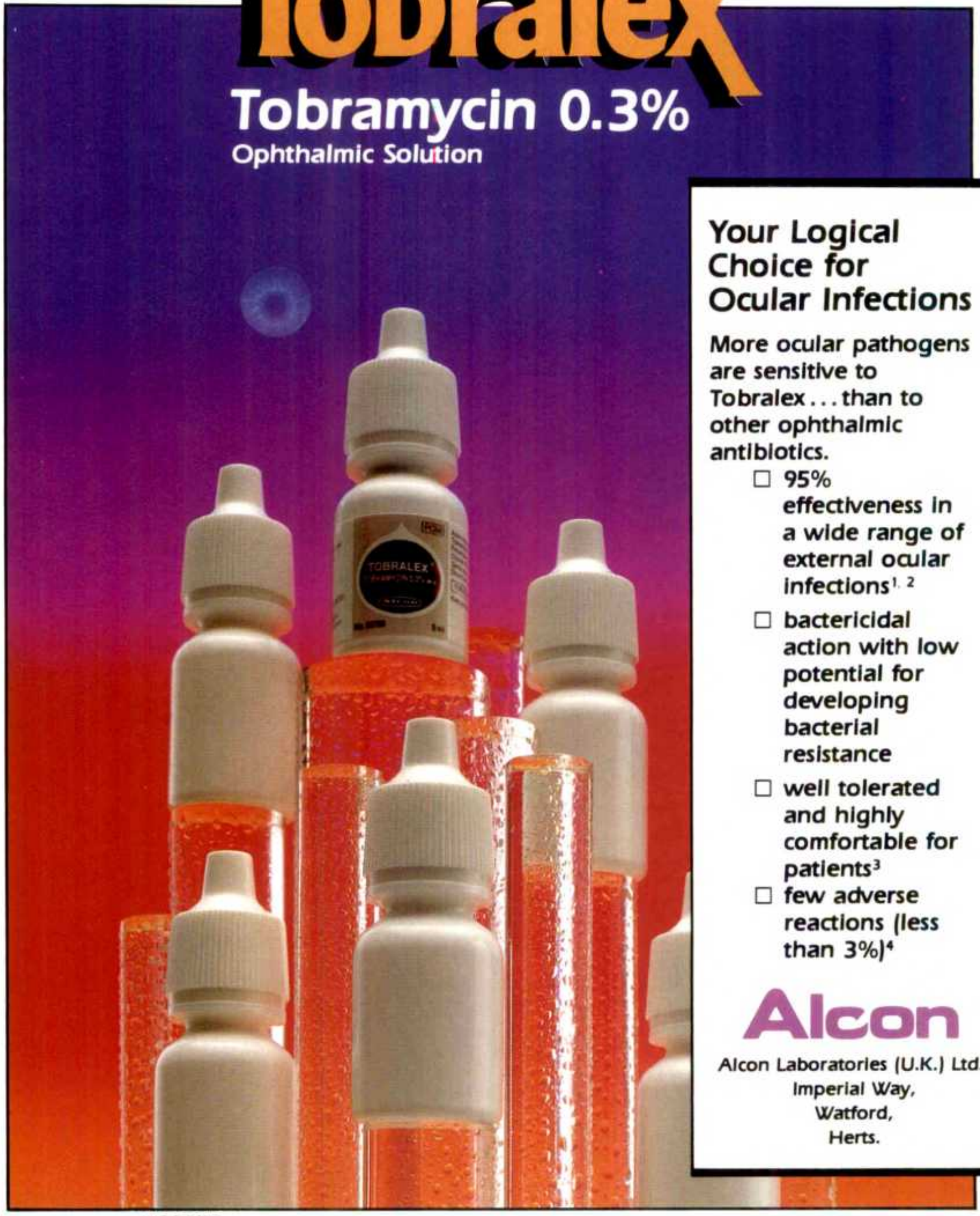

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References: 1. Cagle, G.D. and Abshire, R.L.: "Quantitative Ocular Bacteriology: A Method for the Enumeration and Identification of Bacteria from the Skin Lash Margin and Conjunctiva." Investigative Ophthalmology and Visual Science 20:751-758 (June) 1981. **2.** Data on file, Alcon Laboratories, Inc. **3.** Smith, J.P.: Data on File, Alcon Laboratories, Inc. **4.** Cagle, G. et al.: "Topical Tobramycin and Gentamicin Sulfate in the Treatment of Ocular Infections: Multicenter Study." Current Eye Research 1:523-534, 1982.

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Fuchs's heterochromic cyclitis and posterior capsulotomy

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SUMMARY We report a case of intractable glaucoma following an uncomplicated secondary posterior capsulotomy in a 48-year-old male with Fuchs's heterochromic cyclitis. The patient had been free of inflammation and glaucoma since cataract extraction 27 years previously. We also report the results of phenotypic analysis of lymphocytes removed from the anterior chamber.

The prognosis for successful intraocular procedures in eyes with Fuchs's heterochromic cyclitis has been variously reported. Franceschetti stated that the prognosis for cataract extraction in complicated heterochromia is excellent, perhaps even better than in normal eyes.[1] Smith and O'Connor reported minimal complications in 29 lens extractions in patients with Fuchs's syndrome.[2] Conversely, Ward and Hart considered secondary glaucoma to be the most serious and most common condition associated with cataract extraction in this entity.[3] Norn reported postoperative glaucoma in seven of 19 (36%) patients undergoing cataract extraction for Fuchs's syndrome,[4] and Huber described an abrupt rise in intraocular pressure following anterior chamber puncture in patients with this syndrome.[5]

We describe a protracted rise in intraocular pressure following posterior capsulotomy in an eye with Fuchs's syndrome. The eye had been free of inflammation for 27 years after extracapsular cataract surgery. The glaucoma was relentless and progressive despite medical and surgical management. We report this case to remind clinicians of the postoperative difficulties which can be encountered with this disease, to point out that posterior capsulotomy may not always be a trivial procedure in such cases, and to report a technique for studying the immunocytology of inflammatory cells in the anterior chamber.

Case report

A 48-year-old white male reported to Flinders Medical Centre Eye Clinic on 5 April 1983 with a complaint of poor visual acuity in the right eye. A right extracapsular lens extraction had been done in that eye 27 years previously. Although there was good corrected vision at that time, his right visual acuity had decreased over several years prior to 1983. There had been no episodes of intraocular inflammation or raised pressure since the time of cataract extraction.

Visual acuity was 6/60 in the right eye and 6/5 in the left eye. There was mild heterochromia, the right iris being lighter. The right cornea was clear except for a few fine, white endothelial deposits, and there were no signs of intraocular inflammation. The posterior capsule was moderately opacified, and there were multiple condensations in the right anterior vitreous. Iris transillumination defects were noted in the right eye, and its iris vasculature was clearly visualised owing to atrophic changes of the iris stroma. Intraocular pressure was 12 mmHg by applanation, and the retinal examination was unremarkable. The left eye was normal.

On 9 May 1983 we performed an uncomplicated posterior capsulotomy through a clear corneal incision near the limbus. A trickle of blood, which appeared to originate from the angle opposite the site of entry, was noted during the procedure.

On the first postoperative day there was diffuse microcystic oedema of the corneal epithelium, a moderate aqueous inflammatory response, and a small hyphaema. Intraocular pressure by applanation was 60 mmHg. The raised pressure responded initially to acetazolamide, timolol, and atropine, so that on the following day the intraocular pressure was 20 mmHg, but still with moderate inflammatory signs in the aqueous.

A diagnostic anterior chamber paracentesis was

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performed in an attempt to establish whether the inflammation was a response to previously sequestered lens remnants or to reactivation of the underlying disease. The patient was then started on dexamethasone phosphate 0·1% four times daily in addition to the acetazolamide and timolol. Signs of intraocular inflammation remained unchanged on this regimen, but the intraocular pressure slowly rose, so that by the tenth postoperative day it was consistently between 30 and 40 mmHg, and by the twentieth day it was fluctuating between 40 and 45 mmHg. At this point the patient developed acetazolamide intolerance, and the drug was discontinued. The topical steroid was increased to one drop every two hours for 10 days, then discontinued because it had no effect on the inflammatory signs and so as to eliminate the prospect of steroid responsiveness.

Because of progressive optic nerve head cupping and deterioration of the visual field, a trabeculectomy was performed on 5 September 1983. The patient did well for 18 days with a functioning filter and intraocular pressure less than 10 mmHg, but with continued signs of moderate inflammation in the aqueous in spite of the reinstitution of topical dexamethasone phosphate 0·1% every two hours.

Three weeks later the intraocular pressure had risen to 39 mmHg, with no visible conjunctival bleb and no response to ocular massage. While timolol 0·5% and atropine 0·1% drops were administered twice daily, intraocular pressure remained around 30 mmHg. Because of progressive changes in nerve head and visual field a Molteno tube[6] was inserted in the superotemporal aspect of the chamber angle on 20 October 1983. Intraocular pressures remained less than 10 mmHg until three weeks postoperatively, at which time the intraocular pressure was 40 mmHg, and the tube could no longer be visualised in the chamber angle.

Table 1 *Comparison of lymphocyte surface antigens found in anterior chamber and peripheral blood*

Antibody specificity	*% Positive cells*	
	Anterior chamber	*Peripheral blood*
pan T	100	67
Ia	8	19
T_8	1	24

Further surgery was deferred at the patient's request. The intraocular pressure persisted at around 40 mmHg while on timolol and atropine, and only a small temporal island of visual field remained with total cupping of the optic nerve head.

RESULTS OF ANTERIOR CHAMBER PARACENTESIS

A small volume of anterior chamber aspirate (0·15 ml) was placed in heparinised tissue culture medium and transported to the laboratory for Giemsa cytology and immunoperoxidase staining.[7] Examination of the Giemsa-stained slide revealed predominantly mononuclear cells consisting of 0% neutrophils, 24% monocytes, 75% lymphocytes, and 1% immature lymphocytes (Fig. 1). Immunoperoxidase staining disclosed that 100% of the lymphocytes were positive for a pan T cell marker; 8% were Ia antigen positive and only 1% were T–8 antigen positive (Fig. 2, Table 1).

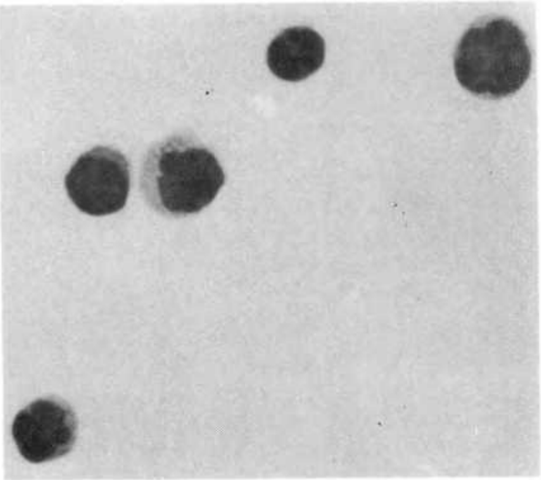

Fig. 1 *Giemsa-stained mononuclear cells from anterior chamber aspirate. (×437).*

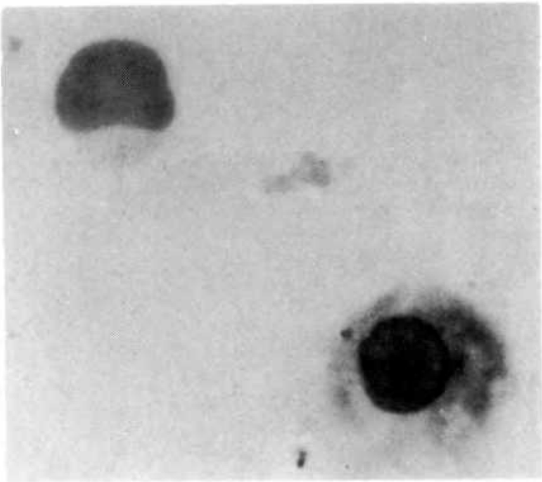

Fig. 2 *Immunoperoxidase staining for Ia antigen. Cell at lower right is Ia antigen positive. (×1165).*

Discussion

The reasons for the postoperative intraocular inflammation and raised intraocular pressure in this patient are unclear. The differential diagnosis for the anterior segment inflammation included either a response to sequestered lens material released at the time of capsulotomy, or early postoperative endophthalmitis, or an exacerbation of the inflammatory signs that are a part of Fuchs's syndrome. We found the anterior chamber paracentesis valuable in that the primarily lymphocytic response made the first two possibilities unlikely. The cytological features in this patient are consistent with those described in Fuchs's syndrome by others[8-11] in that the aqueous of patients with Fuchs's syndrome contains numerous inflammatory cells, primarily of the mononuclear series.

Glaucoma, which proved relentless and devastating in this eye, is reported to occur in from 0 to 56% (average 15%) of eyes with Fuchs's heterochromic cyclitis[12] and represents the most serious complication of the syndrome.

Acute increases of intraocular pressure associated with cataract extraction in eyes with this disease have been reported.[3 4 13] Moreover, an increased pressure following paracentesis was even considered a provocative test for glaucoma in heterochromic cyclitis.[5]

The glaucoma in eyes with Fuchs's syndrome is believed to be due to high outflow resistance caused by trabecular sclerosis.[5] A postoperative rise in intraocular pressure such as that seen in the present case may be due to further embarrassment of already compromised outflow channels by increased numbers of chronic inflammatory cells. We doubt whether the glaucoma was related to steroid responsiveness because the intraocular pressure remained raised for nearly four months after discontinuation of topical dexamethasone prior to trabeculectomy.

The glaucoma associated with Fuchs's syndrome is said to be permanent and generally refractory to medical management but amenable to trephining procedures.[14] Unfortunately our case proved to be resistant to both medical and surgical management, perhaps not surprisingly in the face of continuing inflammation.

Although many authors offer a variety of opinions on the prognosis for intraocular surgery in eyes with Fuchs's heterochromic cyclitis, our case would support the contention that such eyes have potential for developing increased inflammatory signs and glaucoma following intraocular manipulation. Our experience also underscores the notion that glaucoma is the most serious complication in this syndrome and that it can be refractory to successful medical and surgical intervention.

Immunoperoxidase staining is an appropriate way of determining the phenotype of inflammatory cells in anterior chamber fluid. It is more sensitive than immunofluorescence and has the added advantage of providing a permanent staining reaction. The technique can be used on the small number of cells retrievable from the anterior chamber. Whether it is useful to determine the phenotypes of cells in anterior uveitis is under investigation.

Grateful acknowledgement is made to Keryn Williams, Marion Roberts, Julie Ash, and Heddi Zola for their assistance in preparing this paper.

References

1 Franceschetti A. Heterochromic cyclitis (Fuchs' syndrome). *Am J Ophthalmol* 1955; **39:** 50–8.

2 Smith RE, O'Connor R. Cataract extraction in Fuchs sydrome. *Arch Ophthalmol* 1974; **91:** 39–41.

3 Ward DM, Hart CT. Complicated cataract extraction in Fuchs's heterochromic uveitis. *Br J Ophthalmol* 1967; **51:** 530–8.

4 Norn MS. Cataract extraction in Fuchs' heterochromia. *Acta Ophthalmol (Kbh)* 1968; **46:** 685–99.

5 Huber A. Das Glaukom bei komplizierter. Heterochromie Fuchs. *Ophthalmologica* 1961; **141:** 122–35; **142:** 66–115.

6 Ancker E, Molteno ACB. Molteno drainage implant for neovascular glaucoma. *Trans Ophthalmol Soc UK* 1982; **102:** 122–4.

7 Hancock WW, Becker GJ, Atkins RC. A comparison of fixatives and immunohistochemical techniques for use with monoclonal antibodies to cell surface antigens. *Am J Clin Pathol* 1982; **78:** 825.

8 Goldberg MF, Erozan YS, Duke JR, Frost JK. Cytopathologic and histopathologic aspects of Fuchs's heterochromic iridocyclitis. *Arch Ophthalmol* 1965; **74:** 604–9.

9 Matteucci M. Considérations pathogéniques sur l'hétérochromie de Fuchs. *Bull Mem Soc Fr Ophtalmol* 1950; **63:** 220–4.

10 Matteucci M. Considérations pathogéniques sur l'hétérochromie irienne de Fuchs. *Ann Oculist (Paris)* 1951; **184:** 383–403.

11 Verray F. Hétérochromies de l'iris. In: *Clinique de l'humeur aqueuse pathologique*. Neuchatel and Paris: Delachaux and Niestlé, 1954: 214–8.

12 Lowenfeld IE, Thompson HS. Fuchs's heterochromic cyclitis: a critical review of the literature. I. Clinical characteristics of the syndrome. *Surv Ophthalmol* 1973; **17:** 394–457.

13 Sym WG. Heterochromia iridum. *Ophthalmol Rev* 1889; **8:** 202–5.

14 Grant WM. Heterochromic cyclitis (Fuchs). In: Chandler PA, Morton Grant W, eds. *Glaucoma*. Philadelphia: Lea and Febiger, 1979: 247–9.

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Histopathological findings in necropsy eyes with intraocular lenses

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SUMMARY The histopathological findings in five post-mortem eyes with anterior chamber and iris fixation intraocular lenses (IOLS) are discussed. The interval between lens insertion and death ranged from 3½ to 52 months. Clinically the lenses were well tolerated and the surgery was considered to be successful. In one case a vitrectomy was required. Prominent histopathological features included reduced corneal endothelium (five cases), central cornea guttata (one case), dislocation of an anterior chamber IOL (one case), abnormalities of the filtration angle (five cases), non-granulomatous iritis (two cases), and iris atrophy and erosion (five cases).

On 29 November 1949 Harold Ridley implanted the first intraocular lens (IOL).[1] Thirty-five years later intraocular lens implantation is a generally accepted and apparently highly successful means of improving vision after removal of a cataractous lens.[2] Although examination of surgically enucleated eyes has provided some clues to the potential complications occurring with IOLs,[3] a more valid assessment of their effect on the eye can be obtained by studying necropsy eyes in which an IOL has been used.[4] This report describes the histopathological findings in IOL-containing eyes obtained post mortem from 1976 through 1983 at the David G Cogan Eye Pathology Laboratory of the Massachusetts Eye and Ear Infirmary. A total of five eyes were examined (Table 1).

Materials and methods

All specimens included in this study were received from the necropsy service and submitted to the David G Cogan Eye Pathology Laboratory between 1976 and 1983. Clinical data were either extracted from patient records or elicited from the patient's physicians. After measurement and gross dissection, photodocumentation was obtained for all specimens received. The IOLs were removed prior to histopathological processing as atraumatically as possible. Ten pupil-optic nerve sections were cut and stained

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Table 1 *Necropsy eyes after IOL implantation*

	Case number				
	1	*2*	*3*	*4*	*5*
Age	90	74	89	71	89
Sex	M	F	M	M	F
Race	W	W	W	W	W
Extraction (intra- or extracapsular)	E	I	I	I	I
IOL	Binkhorst iris fixation	Wurst-Platina iris fixation	Choyce anterior chamber	Binkhorst iris fixation	Medallion iris fixation
Duration (months)	3½	5½	6½	8	51

with haematoxylin-eosin and periodic acid Schiff and examined independently by three observers.

Results

CASE 1

A 90-year-old white male underwent uncomplicated extracapsular cataract extraction OD with placement of a Binkhorst iris fixation IOL on 7 September 1976. His best corrected preoperative visual acuity was 20/200 OD; postoperative visual acuity was 20/50 with a normal funduscopic examination. After 3½ months' uncomplicated postoperative course he died of carcinoma of the lung.

Gross examination of the right eye showed a well-positioned iris fixation IOL. A well-healed peripheral corneal scar was noted. The IOL was mechanically removed during this examination. The eye was opened in the horizontal meridian. Microscopic examination revealed a well-healed full thickness corneal scar peripherally. The endothelial cell layer was thinned and sparse. The epithelium, Bowman's membrane, stroma, and Descemet's membrane were otherwise normal. The anterior chamber was clear, and the angle appeared recessed on both sides. The iris was atrophic, with a mild chronic non-granulomatous infiltrate. Posterior synechiae to the anterior lens capsule were present. Multiple ciliary body cysts were seen. The retina showed peripheral schisis but was otherwise normal. The vitreous, choroid, sclera, and optic nerve were unremarkable.

CASE 2

A 74-year-old white female with a history of diabetic retinopathy, nephrosclerosis, and generalised atherosclerosis presented on 1 September 1976 with a best corrected visual acuity OD of finger counting at 2 feet (60 cm). She underwent an intracapsular cataract extraction with implantation of a Wurst-Platina iris fixation lens at this time. The procedure was complicated by vitreous loss necessitating anterior vitrectomy. Best corrected postoperative visual acuity remained at a counting fingers level consistent with the retinal changes resulting from severe diabetic retinopathy. She developed secondary glaucoma related to rubeosis and secondary angle closure postoperatively, which was successfully controlled medically. Five and a half months after cataract surgery she died of an acute myocardial infarction.

Gross examination OD revealed a well positioned iris fixation IOL. A peripheral corneal scar was noted. The retina was attached but showed extensive haemorrhages and exudates. Cobblestone degeneration was observed.

On microscopic examination of the right eye Bowman's membrane was intact except in the area of a limbal vascular pannus. Examination of the corneal stroma revealed a well-healed surgical wound with adjacent monofilament sutures. Moderate stromal downgrowth was present near the wound. Descemet's membrane was diffusely thickened. The endothelium was scanty, with flattened cells.

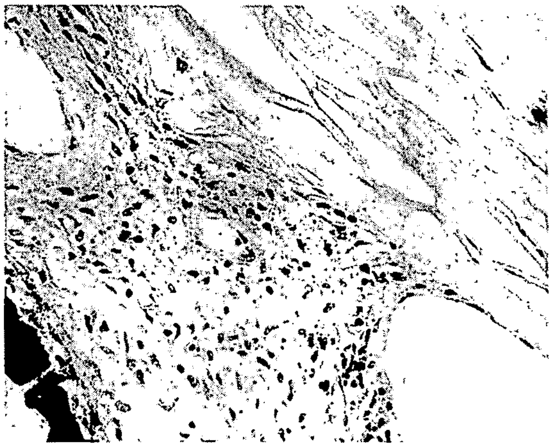


Fig. 1 *Peripheral anterior synechiae in a 74-year-old diabetic female 5½ months after intracapsular cataract extraction with implantation of a Wurst-Platina iris fixation lens. (Haematoxylin and eosin, ×130).*

The entire angle was closed by peripheral anterior synechiae adherent to the site of healed corneal sections, with prominent superficial vessels present (Fig. 1). There was minimal pigment dispersion in an otherwise normal anterior segment. Examination of the iris revealed ectropion uveae with rubeosis, as well as lacy vacuolisation of the pigment epithelium. The ciliary processes were hyalinised.

Strands of formed vitreous were observed. Examination of the retina revealed microaneurysms, deep and superficial haemorrhage, intraretinal oedema, exudates, and peripheral cystoid degeneration. No preretinal neovascularisation or retinal membrane was seen. Multiple drusen were observed. The sclera and optic nerve were unremarkable.

CASE 3

This 89-year-old white male with best corrected visual acuity of 20/200 OU presented for cataract extraction OD on 21 June 1977, at which time an uncomplicated intracapsular extraction was performed OD with insertion of a Choyce anterior chamber lens. The patient did well postoperatively. During his last eye examination four months later the lens was observed to be in place, and his visual acuity was 20/200 OD. The cause of his poor visual acuity was not apparent. He died of an acute myocardial infarction 6½ months after cataract extraction.

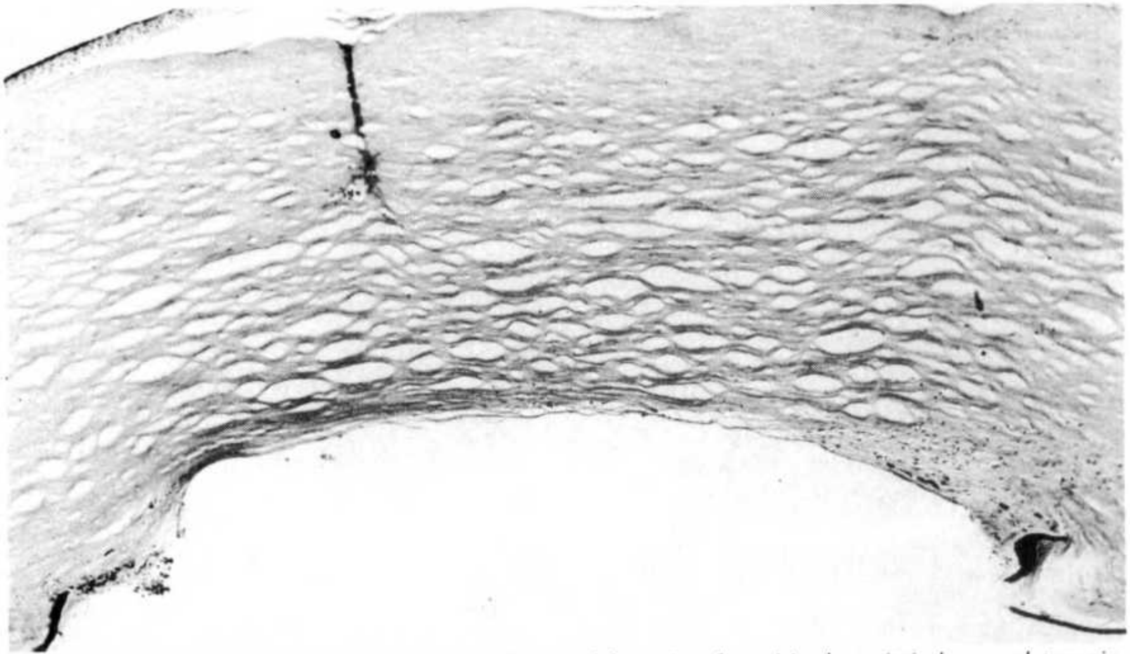


Fig. 2 *Central posterior disruption of Descemet's membrane with formation of a semicircular cavity in the corneal stroma in an 89-year-old male 6½ months after intracapsular cataract extraction with implantation of a Choyce anterior chamber lens. (Periodic acid schiff, ×28).*

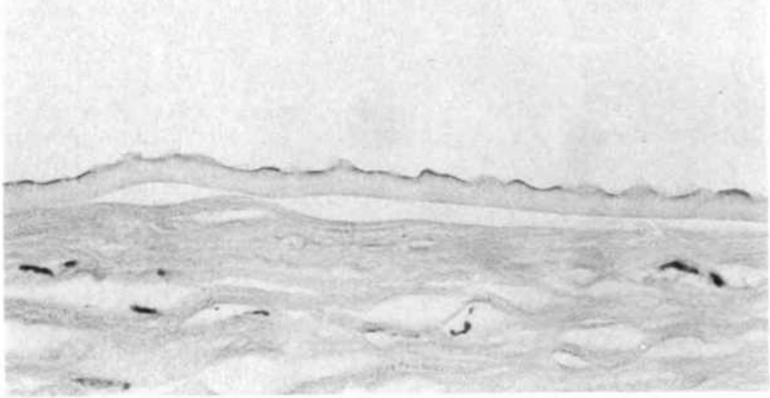
A peripheral corneal scar was noted on gross examination. An IOL was mechanically removed from the anterior segment OD. The iris showed anterior synechial changes with incomplete iridectomy. The optic disc showed physiological cupping.

Microscopic examination of the cornea OD revealed a central posterior disruption of Descemet's membrane, with formation of a semicircular cavity in the stroma surrounded by chronic inflammatory cells (Fig. 2). Peripherally a well-healed stromal scar contained chronic non-granulomatous inflammatory cells, pigment granules, and suture material. An inflammatory pannus was present. The corneal endothelium was sparse, and guttae were present on Descemet's membrane (Fig. 3).

The anterior chamber was clear. The iris was atrophic and showed occasional peripheral anterior synechiae. The ciliary body was within normal limits.

The retina had peripheral cystoid degeneration but was otherwise healthy. The vitreous, choroid, and

Fig. 3 *Central cornea guttata observed in case 3. (Haematoxylin and eosin, ×150).*



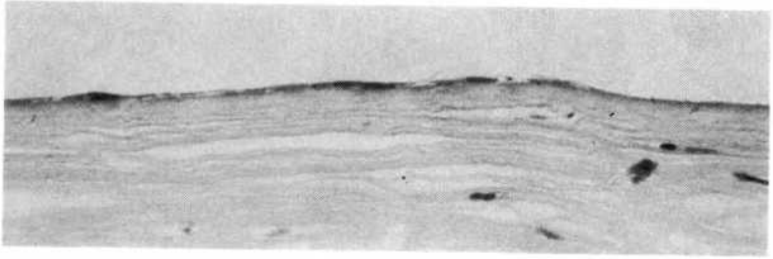


Fig. 4 *A thinned and sparse endothelial cell layer was present in all eyes examined. (Haematoxylin and eosin, ×107).*

sclera appeared normal. The optic nerve showed physiological cupping, with some increased cellularity, but was considered to be within normal limits.

CASE 4

A 71-year-old white man underwent an uncomplicated intracapsular cataract extraction OS with placement of a Binkhorst iris fixation IOL in September 1977. His best corrected preoperative visual acuity was 20/200 OS; postoperative visual acuity was 20/40 OS. After an uncomplicated course he died eight months later of respiratory failure secondary to chronic obstructive lung disease.

Gross examination of the left eye revealed a well-positioned iris fixation IOL. A peripheral corneal scar and a large pars plana cyst were visualised. The pseudophakos was dissolved with chloroform and the haptics removed with forceps.

Microscopic examination of the left cornea revealed epithelial microcyst formation, with degenerative areas of Bowman's membrane. A fibrovascular pannus was noted peripherally. The endothelium was thinned and sparse, with peripheral guttae (Fig. 4).

Extracellular pigment granules were observed in the trabecular meshwork and vitreous. Examination of the iris revealed a mild chronic non-granulomatous inflammatory cell infiltrate of the stroma, focal pigment hyperplasia, areas of pigment epithelium loss, and occasional peripheral anterior synechiae. The ciliary body processes were hyalinised and contained a mild chronic non-granulomatous infiltrate.

Pigment was present on the anterior hyaloid face of the vitreous. Peripheral schisis was observed in the retina, which was otherwise normal. A mild chronic non-granulomatous infiltrate was present in the choroid. The optic nerve and sclera were within normal limits.

CASE 5

On 23 September 1976 an 89-year-old hypertensive white female with best corrected visual acuity of 20/200 OS presented for intracapsular cataract

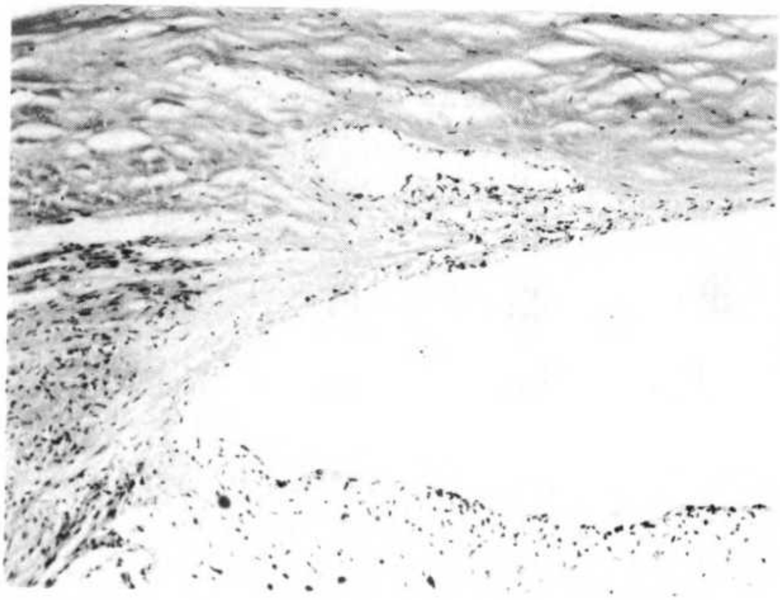


Fig. 5 *Accumulation of pigment in the trabecular meshwork was commonly observed and is thought to be secondary to iris pigment erosion and dispersal. (Haematoxylin and eosin, ×67).*

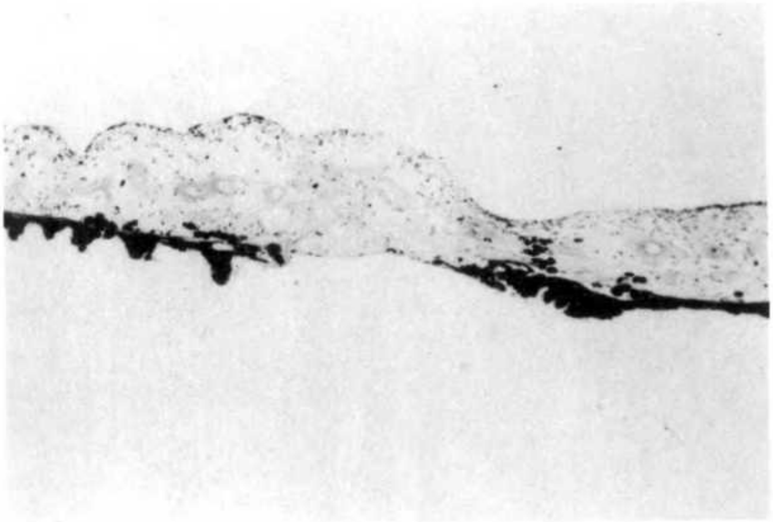


Fig. 6 *Erosion of iris pigment epithelium caused by an iris supported Medallion lens. (Haematoxylin and eosin, ×40).*

extraction with insertion of a Medallion iris fixation IOL. After uncomplicated surgery and postoperative course her visual acuity was 20/20 OS. Fifty-one months after the operation she died of a cardiac arrest.

On gross examination OS a limbal scar was seen. Iris atrophy was present at 1100 to 1200 o'clock. The well-positioned iris fixation IOL was mechanically removed.

Microscopic examination OS revealed a surgical scar at the limbus with poor apposition. Fibrous tissue with pigment granules present filled the gap between the wound edges; the stroma was otherwise normal. A degenerative pannus was present peripherally. Descemet's membrane was fragmented at the posterior aspect of the wound. The endothelial cells were scanty and flattened.

Pigment granules were present in the trabecular meshwork (Fig. 5). The iris was atrophic, with loss of pigment (Fig. 6).

Crystals showing birefringence under cross polarisation and with staining properties consistent with asteroid hyalosis were observed embedded in the amorphous matrix of the vitreous. The retina showed peripheral cystoid degeneration but was otherwise normal. The choroid, sclera, and optic nerve were unremarkable.

Discussion

While the eyes examined in previous studies may provide some clues to the ocular response to IOLs, findings in the specimens studied may be subject to a selection bias by virtue of the fact that the eyes came to enucleation. An additional and probably more realistic histopathological assessment of this procedure comes from the findings based on the examination of necropsy eyes in which an IOL has been used. From the post-mortem findings it would seem that intraocular lenses are well tolerated by the eye so long as there have been no clinical complications.[5] Wolter *et al.*[6] point out that, 'from the viewpoint of the eye pathologist', eyes with IOLs are 'not normal'—but are also 'certainly not sick.' The consequences of IOLs which we have observed in our series of post-mortem eyes include apparent endothelial loss, central cornea guttata, IOL dislocation, abnormalities of the filtration angle, iritis, and iris atrophy and erosion.

The corneal endothelium in these eyes shows variable degrees of cell loss and thinning. Endothelial cell loss is a common accompaniment of intraocular lens insertion and has frequently been attributed to intraocular trauma during lens implantation as well as non-specific adverse effects related to the presence of an IOL.[7-9] With sufficient endothelial damage corneal deturgescence can no longer be maintained, and irreversible oedema occurs. The data presented by Rao *et al.*[9] show progressive endothelial cell damage occurring in eyes with IOLs. In his discussion of this article Leibowitz[9] questioned whether the average age of patients undergoing intraocular lens implantation statistically favours their death before the level of endothelial cell loss reaches the point at which corneal decompensation occurs. The frequency of persistent corneal oedema after intraocular lens implantation has been reported to be 6·2%.[10] In fact corneal transplantation is now more often performed for pseudophakic bullous keratopathy than any other disease. Endothelial cell loss has been claimed to be much less severe in eyes with posterior chamber lenses than in eyes with anterior chamber, iris fixation, or iridocapsular lenses.[11]

The histopathological findings in case 3 are compatible with a partial penetrating injury to the central cornea by the anterior chamber lens. Cameron and Doughman[12] point out that, if mechanical compression on a tissue by an IOL is severe or prolonged or if the fibroproliferative response to the tissue is inadequate, the synthetic material will appear to migrate through the tissue, with resultant erosion. The IOL in this case was last observed in place by an ophthalmologist three months prior to the death of the patient. The dislocation rate of all IOLs has been reported to be about 4%.[13] Iris fixation lenses are known to become dislocated following pupil dilatation.[11 13 14] However, because this patient had an anterior chamber IOL, the role of trauma or a poor fitting IOL should be considered in the aetiology of the dislocation. While luxation into the anterior chamber can produce corneal dystrophy or erosion, dislocation of an IOL into the vitreous cavity can result in macular degeneration or retinal detachment, as well as vitreous loss secondary to surgical attempts at retrieval of the IOL.

Abnormalities of the filtration angle were observed in all cases and included pigment in the trabecular meshwork, angle recession, and angle closure. The cause of the glaucoma in case 2 is difficult to determine. Whether glaucoma was secondary to the vitreous loss or to the presence of an IOL cannot be assessed. Glaucoma has been reported to be responsible for from 21%[15] to 59%[16] of enucleations following cataract surgery with IOLs. While cases 3, 4, and 5 showed signs of pigment dispersion to the trabecular meshwork, these eyes did not develop clinical evidence of glaucoma. Angle recession such as that described in case 1 is believed to occur with anterior chamber IOLs owing to erosion of haptics into the ciliary body. Angle recession often precedes secondary glaucoma because Descemet's membrane and the endothelium gradually extend over the recessed angle and eventually impede aqueous outflow. Peripheral anterior synechia formation, observed in cases 2, 3, and 4, is the most frequent pathogenic mechanism resulting in glaucoma following cataract surgery. Jaffe[14] identifies delayed formation of the anterior chamber as the commonest cause of peripheral anterior synechiae.

Our observation of non-granulomatous chronic inflammation of the iris in cases 1 and 4 is consistent with numerous previous reports describing non-granulomatous iritis with IOLs.[6 17-19] Although the infiltration was located at the site where the lens had been in contact with the iris stroma, it is unclear whether the inflammatory process was due to mechanical and/or toxic irritation. In none of the patients was the iritis sufficiently severe to produce clinical symptoms. It is of note that Kincaid *et al.*[5] have described a conspicuous granulomatous reaction on the anterior iris surface in a post-mortem eye with a well-tolerated anterior chamber lens. No evidence of this was observed in this series.

Iris atrophy and erosion were common findings. Focal loss of pigment epithelium was observed, with dispersal of pigment to the anterior chamber, vitreous, corneal wound, and trabecular meshwork. Iris atrophy and erosion are believed to be due to surgical trauma and to mechanical pressure and friction by the IOL.[19] McDonnell *et al.*[11] have reported that iris atrophy and erosion can be consistent with excellent visual acuity. They note that iris change is not often seen with posterior chamber lenses.

From post-mortem findings it would appear that IOLs are well tolerated by the eye. Although uniform clinical success was achieved in this series after pseudophakos implantation, all necropsy eyes showed histopathological consequences of the insertion and continuing presence of the IOL. The corneal endothelium in all eyes examined showed variable degrees of cell loss and thinning; central cornea guttata was noted in one case. Abnormalities of the filtration angle were observed in all cases and included pigment in the trabecular meshwork, angle recession, and angle closure. There were two cases of non-granulomatous chronic iritis and five cases of iris atrophy and erosion. Histopathological changes in an eye with an anterior chamber IOL were compatible with a partial penetrating injury to the central cornea. Cystoid macular oedema, reported to occur in from 5%[20] to 44%[21] of eyes with IOLs, was not observed in this study. Although the lenses were well tolerated, increased information can be afforded by histopathological examination of post-mortem eyes containing IOLs. The correlation between histopathological findings and type of IOL will help us to draw conclusions on the optimal type of IOL that should be used.

References

1 Ridley H. Intra-ocular acrylic lenses. *Trans Ophthalmol Soc UK* 1951; **71:** 617–21.
2 Stark WJ, Worthen DM, Holladay JT. The FDA report on intraocular lenses. *Ophthalmology* 1983; **90:** 311–7.
3 Spencer WH. Symposium: Complications of modern surgical procedures. Introduction. *Ophthalmology* 1978; **85:** 115.
4 Curtin VT. Cases presented at the joint Verhoeff Society and European Ophthalmic Pathology Society Meeting. Washington, DC. April 1976.
5 Kincaid MC, Green WR, Iliff WJ. Granulomatous reaction to Choyce style intraocular lens. *Ophthalmic Surg* 1982; **13:** 292–9.
6 Wolter JR, Croasdale RE, Bahn CF. Reactions to an anterior

chamber lens two years after implantation. *Ophthalmic Surg* 1980; **11**: 794–800.

7 Bourne WM, Kaufman HE. Endothelial damage associated with intraocular lenses. *Am J Ophthalmol* 1976; **81**: 482–5.

8 Hirst LW, Snip RC, Stark WJ, Maumenee AE. Quantitative corneal endothelial evaluation in intraocular lens implantation and cataract surgery. *Am J Ophthalmol* 1977; **84**: 775–80.

9 Rao GN, Stevens RE, Harris JK, Aquavella JV. Long-term changes in corneal endothelium following intraocular lens implantation. *Ophthalmology* 1981; **88**: 386–97.

10 Berkowitz P, Orton RB, Boyaner D, Brownstein S. Pseudophakic bullous keratopathy; a clinical-pathologic analysis. *Can J Ophthalmol* 1979; **14**: 3–9.

11 McDonnell RJ, Green WR, Maumenee AE, Iliff WJ. Pathology of Intraocular lenses in 33 eyes examined postmortem. *Ophthalmology* 1983; **90**: 386–403.

12 Cameron JD, Doughman DJ. Transcorneal extrusion of an intraocular lens. *Ophthalmology* 1983; **90**: 404–9.

13 Drews RC. Inflammatory response, endophthalmitis, corneal dystrophy, glaucoma, retinal detachment, dislocation, refractive error, lens removal, and enucleation. *Ophthalmology* 1978; **85**: 164–75.

14 Jaffe NS. *Cataract surgery and its complications*. St Louis: Mosby, 1981.

15 Mauriello JA, McLean IW, Wright JD. Loss of eyes after intraocular lens implantation: a clinicopathologic study. *Ophthalmology* 1983; **90**: 378–85.

16 Bresnick GH. Eyes containing anterior chamber acrylic implants: pathologic complications. *Arch Ophthalmol* 1969; **82**: 726–37.

17 Ashton N, Choyce DP. Pathological examination of a human eye containing an anterior chamber acrylic implant. *Br J Ophthalmol* 1959; **43**: 577–83.

18 Ashton N, Boberg-Ans J. Pathology of an aphakic eye containing an anterior chamber implant. *Br J Ophthalmol* 1961; **45**: 543–9.

19 Manshot WA. Histopathology of eyes containing Binkhorst lenses. *Am J Ophthalmol* 1974; **77**: 865–71.

20 Pearce JL. Long-term results of the Binkhorst iris clip lens in senile cataract. *Br J Ophthalmol* 1972; **56**: 319–31.

21 Winslow RL, Taylor BC, Harris WS. A one-year follow-up of cystoid macular edema following intraocular lens implantation. *Ophthalmology* 1978; **85**: 190–6.

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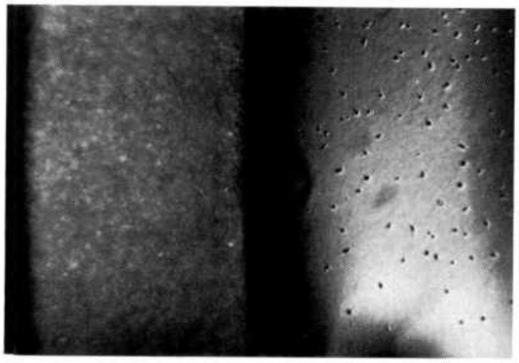

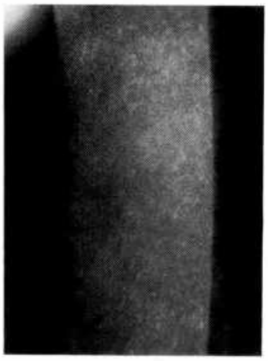

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Cataracts in childhood leukaemia

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SUMMARY The incidence and severity of cataract were studied in 37 children who had completed treatment for acute lymphoblastic leukaemia. Twelve (32%) had posterior subcapsular lens opacities. Treatment had included corticosteroids and cranial irradiation, but no dose relationship was evident. The boys were more severely affected than the girls. Although none of the lens opacities was optically significant, clinicians should be aware of the potential risk to vision.

Following a recent observation in the United States that three out of 50 treated leukaemic children had small and asymptomatic posterior subcapsular lens opacities it was decided to examine the eyes of children treated for acute lymphoblastic leukaemia at the Hospital for Sick Children, Bristol.[1]

Corticosteroids have a well established role in the treatment of leukaemia, and cranial irradiation is now routinely used to prevent meningeal relapse. Since both ionising radiation and steroids are cataractogenic, particular attention was paid to these factors.

Patients and methods

All children who had completed treatment and remained in remission were asked to attend for examination. Best corrected acuities were obtained and pupils dilated with cyclopentolate to allow detailed examination of the lens and retina.

Lens opacities were assessed with a slit-lamp and direct ophthalmoscope and were then carefully drawn to allow sequential assessment. Opacities were graded according to Crews' classification,[2] and, after taking into account other relevant factors such as squint or amblyopia, an estimate of the optical significance of the cataracts was made.

All assessments were made by one examiner, who was unaware of treatment protocols.

Results

In response to 38 postal requests 37 children aged between 8 and 22 years attended for examination, their disease having been diagnosed between 1967 and 1979. All were in remission and off treatment.

Seven of the 14 boys had evidence of posterior subcapsular cataract, but only five out of the 23 girls were so affected. A total of 12 children (32%) had lens opacity.

Crews[2] divided adult steroid induced cataract into four grades of severity. Only grades I (occasional posterior subcapsular opacities or vacuoles in the central region with or without distortion of the specular reflex) and II (small clusters of posterior subcapsular opacities remaining discrete) were seen. Details are given in Table 1.

All children had received steroids in various dosages and protocols. There was no dosage difference between affected and unaffected children (Table 2). A wide range of dosage was represented in each group. As little as 1·1 g/m^2 prednisone was associated with cataract, yet one child received 17·6 g/m^2 without ill effect. Mean daily dosages were not compared in view of the pulsed nature of the treatment.

Likewise both groups had similar doses of cranial irradiation, though the range of dosage was, as

Table 1 *Grades of severity of cataract in affected children*

Patient No.	*Boys*		*Patient No.*	*Girls*	
	Right	*Left*		*Right*	*Left*
1	II	II	8	I	I
2	II	II	9	I	O
3	I	II	10	I	O
4	I	I	11	I	O
5	I	I	12	I	O
6	I	O			
7	O	I			

Correspondence to Dr A J Elliott, Bristol Eye Hospital, Outpatients Department, BRI Yard, Lower Maudlin Street, Bristol 1.

Table 2 *Total steroid dose and total cranial irradiation dose (nominal)*

	Prednisone g/m²	*cGy*
Lens opacities	6·5 (1·1–15·3)	2290 (2000–2400)
Normal	5·2 (1·1–17·6)	1940 (1800–2400), and 3 patients received none

Table 3 *Average age at diagnosis of leukaemia and time after cessation of treatment*

	Age at diagnosis (yr)	*Time off treatment (yr)*
Lens opacities	5·2 (1·8–11)	5·8 (2–10·5)
Normal	6·7 (1·8–15.1)	5·1 (0·3–10.4)

expected, much smaller. The only three children who received no cranial prophylaxis did not have lens opacities. Development of cataract could not be correlated with the radiation field geometry, fractionation, type of machine used, use of sedation, or the observation of restlessness during radiotherapy.

Those with lens opacities were on average younger at the time of diagnosis, but this difference was not significant (Table 3).

One boy with bilateral grade II lens opacities had a visual acuity of 6/15 in each eye, but he was also mentally retarded and highly myopic, and it was considered that the opacities were not fully responsible. The other boys with grade II cataracts had an acuity of 6/6 in each eye.

Discussion

With increasing acceptance that childhood leukaemia is no longer an inevitably fatal disease more attention is being focused on the long-term complications of treatment.[3] Posterior subcapsular cataract appears to be one of these, though fortunately the visual consequences have been slight.

It is presumed that lens opacities result from a toxic effect of various therapeutic agents on the lens. Many agents have ocular toxicity[4]; this study has examined two of the most likely candidates.

Black *et al.* first observed the cataractogenic property of steroids in patients with rheumatoid arthritis.[5] Males predominated, though this finding was not analysed further. Crews confirmed the original observation and noticed a dose relationship.[2] Dikshit and Avasthi[6] made a similar observation in children with nephrotic syndrome treated with corticosteroids, and other authors have since contributed their observations.[7–9]

The dose relationship has not been observed so consistently as in adults, and a recent study in Leeds did not show such a relationship in children with nephrotic syndrome[10]; 14% had cataract and in only one child was vision reduced (to 6/9).

The pathogenesis of steroid cataract remains unclear and there is no animal model.[11]

The incidence, severity, and localisation of the lens opacities in this study are consistent with a steroid aetiology, but the slight trend to unilaterality raises the possibility of a lateralising cause such as cranial irradiation applied asymmetrically due to head movement or tilt. Even with precise screening the lens would receive a small dose, due both to attenuation of the beam by the shielding and to scatter. *X*-irradiation causes posterior subcapsular cataract indistinguishable from those observed in this study. Merriam and Focht[12] have extensively studied the subject and correlated severity and time of onset with dosage. The mechanism appears to be inhibition of mitosis in the germinative epithelium of the lens causing cortical opacities after a latent period. The minimum cataractogenic dose in adults is about 200 cGy, but no detailed data exist for children, in whom the lens may be more sensitive.[12,13]

Examination of two potential cataractogenic influences in this study has revealed no clear aetiology of lens opacities in treated leukaemia. A combination effect would be feasible. Individual susceptibility of certain children is also possible and has been suggested before in reference to steroid cataract.[6,10] Whatever the mechanism, lens opacities do occur and it is important that clinicians should be aware of the potential threat to sight.

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References

1 Nesbit ME, Robison LL, Sather HN, Meadows AT, Ortega JA, Hammond GD. Follow up study of long-term survivors of childhood acute lymphoblastic leukaemia. Childrens Cancer Study Group, Los Angeles 3rd International Symposium on Therapy of Acute Leukaemias 1982 Rome, Italy.

2 Crews SJ. Posterior subcapsular lens opacities in patients on long term corticosteroid therapy. *Br Med J* 1963; **i:** 1644–7.

3 Chessells J. *Recent advances in paediatrics 6.* Edinburgh: Churchill Livingstone, 1981: 157–77.

4 Fraunfelder FT, Meyer SM. Ocular toxicity of antineoplastic agents. *Ophthalmology* 1983; **90:** 1–3.

5 Black RL, Oglesby RB, von Sallman L, Bunim JJ. Posterior subcapsular cataracts induced by corticosteroids in patients with rheumatoid arthritis. *JAMA* 1960; **174:** 166–71.

6 Dikshit SK, Avasthi PN. Posterior lenticular opacities in children on corticosteroid therapy. *Indian J Pediatr* 1965; **32:** 93–96.

7 Havre DC. Cataracts in children on long term corticosteroid therapy. *Arch Ophthalmol* 1965; **73:** 818–21.

8 Kobayashi Y, Akaishi K, Nishio T, Kobayshi Y, Kimura Y, Nagata M. Posterior subcapsular cataract in nephrotic children receiving steroid therapy. *Am J Dis Child* 1974; **128:** 671–3.

9 Fine RN, Offner G, Wilson WA, Mickey MR, Pennisi AJ, Malekzadeh MH. Posterior subcapsular cataracts: post-transplantation in children. *Ann Surg* 1975; **182:** 585–9.

10 Brocklebank JT, Harcourt RB, Meadow SR. Corticosteroid-induced cataracts in idiopathic nephrotic syndrome. *Arch Dis Child* 1982; **53:** 30–4.

11 von Sallmann L, Caravaggio LL, Collins EM, Weaver K. Examination of lenses of steroid-treated rats. *Am J Ophthalmol* 1960; **50:** 1147–51.

12 Merriam GR, Focht EF. Clinical study of radiation cataracts and the relationship to dose. *AJR* 1957; **77:** 759–85.

13 MacFaul PA, Bedford MA. Ocular complications after therapeutic irradiation. *Br J Ophthalmol* 1970; **54:** 237–47.

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Electrolyte imbalances in the aqueous humour in retinoblastoma

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SUMMARY The sodium and potassium concentrations and the lactic dehydrogenase (LDH) activity were estimated in the aqueous and serum of five children with retinoblastoma. Two patients who had a high aqueous LDH activity also showed grossly elevated potassium levels in their aqueous. Though the exact reason for this high potassium concentration in the aqueous is not apparent, it seems likely that cell necrosis within the tumour mass was a contributory factor. It is unlikely that aqueous electrolyte estimations in retinoblastoma could prove to be of any diagnostic value.

The fact that malignant cells in a retinoblastoma secrete various enzymes which by forward diffusion pass into the aqueous and reach significantly higher concentrations in the aqueous than in the plasma was demonstrated by Dias *et al.*[1] This aqueous plasma imbalance has been confirmed by several other workers[2-6] and is of diagnostic significance.

It is also likely that electrolytes, notably potassium, may accompany these enzymes out of malignant cells into the aqueous. As there is no reference in the available literature regarding the electrolyte concentrations in the aqueous in patients with retinoblastoma, it was decided to determine whether electrolyte imbalances do occur between the aqueous and plasma and if so whether these could be of diagnostic value in retinoblastoma.

Materials and methods

Aqueous humour was collected by aqueous puncture from five children coming up for enucleation for clinically diagnosed retinoblastoma at the Victoria Memorial Eye Hospital, Colombo. The aqueous was collected while the patient was under general anaesthesia just prior to enucleation, and great care was exercised to see that none of the specimens was contaminated with blood. Five ml of blood was also removed from the median cubital vein for biochemical investigations. The sodium and potassium concentrations and the lactic dehydrogenase (LDH) activity in the aqueous and plasma were estimated within four hours of collection of the samples.

Sodium and potassium concentrations were measured by flame photometry after 1 in 100 dilution. LDH activity was estimated by the colorimetric method of King,[7] in which the increase in optical density at 340 nm was measured. A unit of activity is the amount of LDH which reduces 1 μmole lactate to 1 μmole pyruvate in 15 minutes at 37°C. Activity is expressed in units per dl (SI conversion: units/l= units/dl×10).

Results

The electrolyte concentrations and LDH activity in the aqueous and serum in the five patients with retinoblastoma are shown in Table 1. The LDH aqueous/serum ratio was raised in all specimens. A

Table 1 *Electrolyte concentrations and LDH activity in aqueous and serum in five patients with retinoblastoma*

Age	*Sex*	*Aqueous humour*			*Serum*		
		Na (mmol/l)	*K*	*LDH Units*	*Na (mmol/l)*	*K*	*LDH Units*
9 months	M	170	64·1	7000	148	4·8	160
1 yr 3 months	M	136	4·5	3450	140	4·6	90
1 yr 8 months	M	170	5·6	1660	148	3·9	310
2 yr 4 months	F	141	4·8	1890	152	4·8	240
11 months	M	164	39·5	4280	146	4·2	195

significant finding was a grossly raised aqueous potassium concentration in two of the specimens.

Subsequent histological examination of the enucleated eyes confirmed the presence of retinoblastoma, and all specimens showed areas of necrosis and calcification. Apart from this there was nothing else of any histological significance in any of the specimens.

Discussion

The reason for this electrolyte anomaly in the aqueous is not clear. Potassium is known to be secreted by the ciliary processes into the aqueous. In patients with retinoblastoma the intraocular tension is high, and it is likely that the ciliary body is compressed, and the ciliary secretion would, if anything, be reduced.

A differential drainage mechanism for potassium which is altered in some way in retinoblastoma is also possible. If this were so, then all patients with retinoblastoma should show an abnormal increase of potassium in their aqueous.

A potassium concentration of 64·1 mmol/1 was detected in the child who had an aqueous humour LDH activity of 7000 U, which was the highest LDH activity recorded in this laboratory. The second child who had a high potassium concentration of 39·5 mmol/1 also showed a very high LDH activity in the aqueous, but there appeared to be no correlation between the aqueous potassium concentration and the LDH activity in the other specimens.

Possibly a high LDH activity is associated with greater necrosis of the tumour mass,[8] and this could be the reason for the increased potassium concentration in the aqueous. Necrotic cells probably release their intracellular potassium, which diffuses through the vitreous into the aqueous, but it is difficult to understand why an increase in potassium was not observed in all specimens.

A histological survey of the specimens failed to show a correlation between the extent of necrosis and the potassium concentration in the aqueous.

It is difficult to pinpoint the reason for the significant increase of the potassium concentration in the aqueous in these two patients, and, though unlikely to be of diagnostic significance, it could be of pathophysiological significance. It is intended to perform electrolyte estimations on a much larger sample to determine the cause of the raised potassium concentration in the aqueous humour in patients with retinoblastoma.

I thank the University of Colombo for financial support and Mrs V S B C Fernando for secretarial assistance.

References

1 Dias PLR, Shanmuganathan SS, Rajaratnam M. Lactic dehydrogenase activity of aqueous humour in retinoblastoma. *Br J Ophthalmol* 1971; **55:** 130–2.

2 Felberg NT, McFall R, Shields JA. Aqueous humour enzyme patterns in retinoblastoma. *Invest Ophthalmol Visual Sci* 1977; **16:** 1039–46.

3 Kabak J, Romano PE. Aqueous humour lactic dehydrogenase isoenzymes in retinoblastoma. *Br J Ophthalmol* 1975; **59:** 268–9.

4 Kaneko A, Suzuki H. Lactic dehydrogenase activity and isoenzymes in retinoblastoma. *Nippon Ganka Gakkai Zasshi* 1972; **76:** 672–5.

5 Swartz M, Herbst RW, Goldberg MF. Aqueous humour lactic acid dehydrogenase in retinoblastoma. *Am J Ophthalmol* 1974; **78:** 612–7.

6 Aksu G. Aqueous humour lactic dehydrogenase activity in normal and diseased eyes. *Ann Ophthalmol* 1981; **13:** 1067–8.

7 King J. A routine method for the estimation of lactic dehydrogenase activity. *J Med Lab Technol* 1959; **16:** 265–72.

8 Dias PLR. Correlation of aqueous humour lactic acid dehydrogenase activity with intraocular pathology. *Br J Ophthalmol* 1979; **63:** 574–7.

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Lacrimal canalicular papillomatosis

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SUMMARY Three new cases of lacrimal canalicular papillomatosis are reported and the total of 12 cases in the literature reviewed. They present with epiphora or a local mass. Multiple recurrences over many years is characteristic. A minority have papillomata of the conjunctiva or lacrimal sac. Histopathological examination shows a benign papilloma with a fibrovascular stalk. Treatment was either multiple excision or cryotherapy, but neither affected the rate of occurrence. A viral aetiology is postulated in some cases.

Lacrimal canalicular papillomatosis was first described by Demaiens in 1818.[1] The aetiology and management remain obscure. We report three cases seen in the Lacrimal Clinic at Moorfields Eye Hospital, London, and review previously reported cases.

Case reports

CASE 1

A 9-year-old West Indian girl presented with a four-month history of right epiphora and was found to have a mass protruding from the right lower punctum. There was nothing of note in the past ophthalmic or medical history. The mass was explored by a canaliculostomy. The canaliculus was seen to be grossly distended, and a papilloma originated from a stalk attached to the epithelium of the lacrimal canalicular ampulla. The papilloma was shaved off. Two months later it recurred at the same site and was similarly treated. Two months later it again recurred at the same site. (Syringing and a dacryocystogram suggested an obstruction at the lower end of the sac.) The papilloma was excised, the lacrimal sac was explored and found to have mucosal thickening, but no papillomata were seen. Six months later it recurred at the same site and an additional papilloma was seen arising from the superior canaliculus. Both were excised. At operation the superior papilloma was found to originate from the middle of the superior canaliculus and the inferior to originate from the ampulla. Cryotherapy was applied to the base of each. One month later it recurred and was seen to grow 4 mm in two weeks prior to excision (Figs. 1 and 2). Both were again excised, but more extensive double freeze cryotherapy was applied. She was last seen four months after this and there was no further recurrence, but there was depigmentation of the skin and canalicular blockage. At no stage was she seen to have papillomata of the conjunctiva.

The histology of all the specimens showed a squamous papilloma (Fig. 3). There was no cellular atypia, koilocytosis, or nuclear inclusion bodies. Electron microscopy did not show any virus-like particles. Viral cultures of the lesions and viral serology were negative on two occasions. The white blood cell count and a standard set of immunological tests were within normal limits.

CASE 2

A 39-year-old Guyanan male resident in England presented with a mass on the tarsal conjunctival aspect of the right upper lid which had been present for three weeks. He was otherwise well. This was excised and found to be a squamous papilloma. Seven months later it recurred at the same site, and additional papillomata were seen growing out of the superior and inferior puncta. At canaliculostomy these were found to originate from the ampulla of the canaliculus. All were excised. During the next five years the canalicular lesions recurred on 11 occasions at intervals of one to nine months, and on two occasions additional lesions of the tarsal conjunctiva recurred. All recurrences were excised at the base. On four occasions cryotherapy was applied to the base but it did not appear to modify the recurrence. On one occasion radiotherapy was given 3600 R to the inner canthus and 2400 R to the lid, but the papillomata continued to enlarge for six months after

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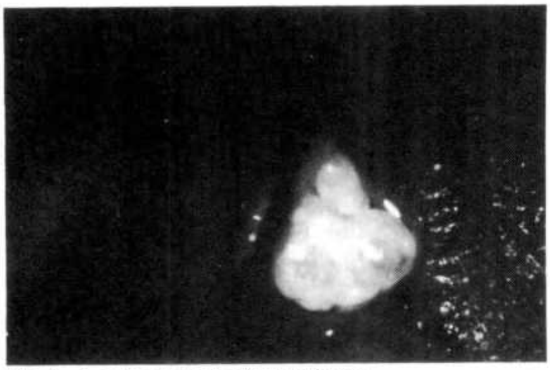

Fig. 1 *Lacrimal canalicular papilloma.*

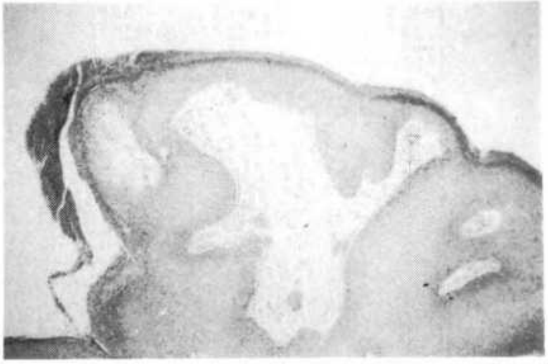

Fig. 3 *Lacrimal canalicular papilloma. (Haematoxylin and eosin, × 85.)*

this and were then excised. During this period dacryocystograms did not reveal any filling defects of the lacrimal sac.

There was then a respite of four years until he again developed symptoms at the age of 48, nine years after the original presentation. For three months he suffered mucous discharge from the previously treated right eye. A hard mass was palpable in the region of the lacrimal sac, and a dacryocystogram (Fig. 4) showed filling defects of the lacrimal sac compatible with mutiple papillomata. He was treated with trifluorothymidine drops five times daily for two months with no relief. He then additionally developed recurrent papilloma of the tarsal conjunctiva. A dacryocystorhinostomy was performed and the lacrimal sac was found to be full of papillomata. All were excised along with the conjunctival papilloma and cryotherapy applied to their bases. Three months later, a small mass was noted in the inferior end of the incision scar. This was excised and found to be an intramuscular papilloma not communicating with the mucosa. Three months later there was a recurrence on the tarsal conjunctiva, which was excised and the base treated with cryotherapy. Eight months after this there was a recurrence in the superior canaliculus and a papilloma in the nose arising from the mucosa at the site of the previous dacryocystorhinostomy. Both were excised and treated with cryotherapy. He was last examined 10 years after this, and there were no further recurrences or further tumours. The histopathology on all specimens was similar to the first case.

CASE 3

A 24-year-old white male presented with a two-month history of unilateral epiphora. Twelve years previously he had a squamous papilloma of the tongue, but there was nothing else of note in the previous medical history. On examination papillomata were protruding from the superior and inferior puncta. There were no conjunctival papillomata. Canaliculostomy was performed, and both papillomata were seen to originate from stalks attached to

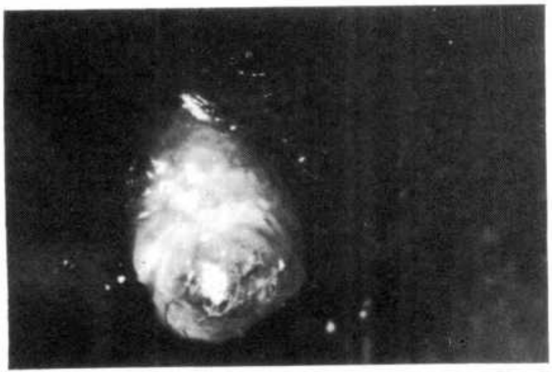

Fig. 2 *Lacrimal canalicular papilloma: same case as Fig. 1 after elapse of two weeks.*

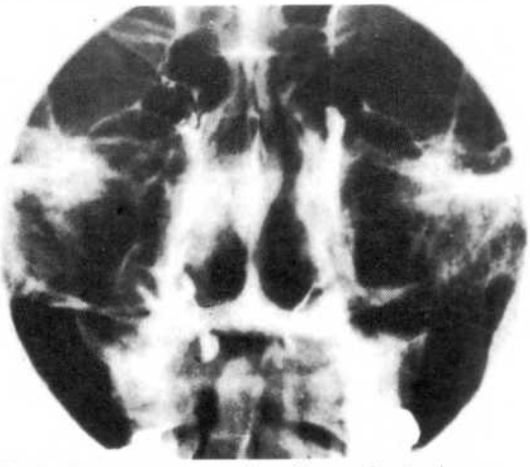

Fig. 4 *Dacryocystogram of papillomata lacrimal sac associated with papillomata of lacrimal canaliculus.*

Table 1 *Previously reported cases*

Author, reference number	*Patient's age*	*Patient's sex*	*Side lesion*	*Canal-inculus involved*	*Total length history*	*Total No. recurrences*	*Treatment*	*Response to treatment*
Anderson[2]	62	M	Left	Lower	3 weeks	Nil	Excision	No recurrences
Aubineau[3]	50	M	Left	Upper	1 Year	Nil	Excision	No recurrences
Ayres[4]	?	F	Right	Lower	1 Year	—	Excision	—
Burke[5]	74	M	Right	Lower	—	—	Excision	—
Camera and Quintana[6]	11	M	Right	Lower	2½ Years	1	Excision	Recurred 3 months
							Excision and cryotherapy	No recurrence
Corticelli *et al.*[7]	15	—	—	—	9 Years	2	Excision	Recurred 6 years
							Excision	Recurred 3 years
							Excision	No recurrence
	14	F	Right	Lower	9 Years	4	Excision × 4	Recurrence × 3
Juler[8]	—	—	Left	Upper	—	—	Excision	—
Libby[9]	40	F	Right	Lower	2 Years	9	Pulled off	Recurred 2 days
							Excision × 7	Recurred 2 days × 7
							Excision and curettage and syringing boric acid	No recurrence
Maruko and Nakagawa[10]	12	M	Left	Lower	—	Nil	Excision	No recurrence
Nicoletti[11]	33	M	Left	Lower	10 Days	Nil	Excision	No recurrence

the ampulla of the canaliculi. These were excised and cryotherapy was applied. The canaliculi and nasolacrimal duct were probed and found patent to the nose. The pathology was similar to that in cases 1 and 2, and electron microscopy did not reveal virus-like particles. There was no recurrence for three years after surgery and he was then lost to follow-up.

PREVIOUSLY REPORTED CASES

The previously reported cases are summarised in Table 1.[2-10]

Discussion

The cases reported here show that lacrimal canalicular papillomata are not usually associated with papillomata of the conjunctiva or lacrimal sac but a minority may be. They are usually unilateral, present with epiphora, with or without a mass, and occur at all ages, and the natural history is one of multiple recurrences over many years.

Human papilloma virus is a DNA virus; it may be implicated in lacrimal canalicular papillomatosis.

Eleven serotypes occur and have been linked with papilloma of the skin, larynx, and genitalia.[11] Evidence of papilloma virus causing conjunctival papillomata is accumulating from histological appearances, immunofluorescent staining of specimens,[12] and DNA molecular hybridization.[13] Papilloma virus may cause some cases of conjunctival papillomata. However, the detection of viruses is much less frequent than in other papillomata, and, if they are a causative factor, the serotype is as yet unknown. The coexistence in some cases of lacrimal canalicular papillomata may also be caused by the papilloma virus. Failure to demonstrate papilloma virus in lacrimal canalicular papillomatosis by either electron microscopy or viral culture does not exclude a viral aetiology, as these techniques are difficult in this group of viruses. However, koilocytosis and nuclear inclusion bodies are histopathological features suggesting a viral cause.[12] These are absent in lacrimal canalicular papillomata, which may be considered a factor against a viral aetiology. Features of conjunctival papillomata have been listed suggesting that some are of viral origin and some are of another cause.[14] Extrapolation of these features to the lacrimal canalicular papillomatosis is unhelpful, as the young age, multiple recurrences, and spontaneous resolution suggest a viral aetiology, whereas the unilaterality, long history, and non-transmissibility suggest some other aetiology in the same cases. Confirmation of a viral aetiology is important, as evidence is now accumulating that some papilloma viruses predispose to malignancy.[11 15] As yet there is no report of the lacrimal canalicular papillomata undergoing malignant transformation.

Treatment of lacrimal canalicular papillomata is to expose the base and excise the papilloma. Cryotherapy has been shown to be an effective alternative treatment of conjunctival papillomata[16-18] and may be considered in lacrimal canalicular papillomata. An attempt at cryotherapy of lacrimal canalicular papillomata would also necessitate canaliculostomy to expose the base of the papilloma, and it has not been reported as the sole treatment. Antiviral chemotherapy has only once been tried and was ineffective, as new papillomata grew while it was being given, and there was no effect on the existing papillomata. The methods tried to prevent recurrence, cryotherapy, and radiotherapy have not been shown to be successful and may lead to local complications.

References

1 Demains AP. Traité des maladies des yeux. Paris: Chez L'auteur et Crochard, 1818; **2:** 92.

2 Anderson DR. Unilateral epiphora caused by papilloma of lower canaliculus. *Arch Ophthalmol* 1967; **78:** 618–20.

3 Aubineau E. Polypes du canalicule lacrymal superior. *Arch Ophthalmol* 1923; **40:** 228–31.

4 Ayres SC. Polypus of lower canaliculus. *Arch Ophthalmol* 1903; **32:** 369–71.

5 Burke JW. Papilloma lying within lower canaliculus. *Am J Ophthalmol* 1938; **21:** 189.

6 Camara J, Quintana M. Canaliculitis papillomatosa. *Arch Soc Espanol Oftalmol* 1975; **35:** 173–8.

7 Cotticelli L, Savastano S, Romano A, Dimeo A. Papilloma del canalicolo lacrimale inferior. *Boll Occulist* 1978; **57:** 75–8.

8 Juler FA. A papilloma in the upper canaliculus. *Trans Ophthalmol Soc UK* 1975; **35:** 243–4.

9 Libby GF. Polyps in the lower canaliculus. *Ophthalmic Record* 1904; **13:** 368–70.

10 Maruko H, Nakagawa T. A case of primary papilloma of lacrimal canaliculus. *Folia Ophthalmol Jpn* 1977; **27:** 937–9.

11 Niccoletti G. Papilloma del canaliculo lacrimale inferior. *Ann Ottalmol Clin Oculist* 1926; **12:** 24–6.

12 Howley, DM. The human papilloma virus. *Arch Pathol Lab Med* 1982; **106:** 429–32.

13 Lass JH, Jenson AB, Papale JJ, Albert DM, Papilloma virus in human conjunctival papillomas. *Am J Ophthalmol* 1983; **95:** 364–8.

14 Lass JH, Grove AS, Papale JJ, *et al.* Detection of human papilloma virus DNA. Sequences in conjunctival papillomata. *Am J Ophthalmol* 1983; **96:** 670–4.

15 Wilson FM, Ostler HB. Conjunctival papillomata in siblings. *Am J Ophthalmol* 1974; **77:** 103–7.

16 Singer A, Walker PG, McCance DS. Genital wart virus infection. *Br Med J* 1984; **282:** 735–7.

17 Harkey NE, Netz HS. Cryotherapy of conjunctival papillomas. *Am J Ophthalmol* 1968; **66:** 872–4.

18 Omohundro JM, Elliott JH. Cryotherapy of conjunctival papillomas. *Arch Ophthalmol* 1970; **84:** 609–10.

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Fast and slow artificial diurnal rhythms (light–darkness–light) and the rate of progression of retinal degeneration in dystrophic RCS rats. An electroretinographic study

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SUMMARY The RCS rat strain is characterized by a hereditary progressive degeneration of retina and pigment epithelium. The possible influence of varying artificial diurnal rhythms on the rate of progression of the degeneration was investigated with electroretinography (ERG). Light intensity of the 'day'-periods and the total light exposure were constant in two groups of RCS rats subjected to 2 h light/2 h darkness and to 24 h light/24 h darkness periods respectively. No difference in the rate of degeneration as mirrored by the ERG was seen between the two groups. The ERGs were unrecordable after 7–8 weeks, and the experiments started at birth. No changes in the ERG of controls, genetically identical with the RCS strain except for the retinal dystrophy gene, were seen when they were subjected to the two diurnal rhythms. The results lessen the probability that careful long-term patching of an eye in patients with retinitis pigmentosa or other related hereditary degenerative diseases (in order to diminish the influence of diurnal illumination changes leading to shedding of receptor outer segments) will halt or modify the progression of the disease in man.

Rodent diseases causing photoreceptor degeneration were described by Keeler[1] in mice and by Bourne *et al.*[2] in RCS (Royal College of Surgeons) rats. The degeneration in the rat shares with certain human retinal degenerations the features of heritability, destruction of photoreceptor cells, migration of pigment epithelial cells into the neural retina in the late stages of the disease, and other similar end-stage pathological features.[3] The RCS rat is currently being studied as one of several possible animal models for human retinitis pigmentosa at several research centres. These animals are characterised by a disorder in the pigment epithelium surrounding the neuroretina: a lack of phagocytosis of shed rod outer segment discs leads to the accumulation of debris between the pigment epithelium and the retina. This causes a secondary destruction of the neuroretina.[4] The pathogenesis of the group of human eye disorders called retinitis pigmentosa is probably manifold, but a defect in phagocytosis of the pigment epithelium might exist in some subgroups of retinitis pigmentosa or related diseases.

The effects of various ambient light conditions on the rate of progression of the retinal degeneration in RCS rats have been studied by a number of researchers.[5-7] Strong light precipitates an early onset of the degeneration and a faster decline in retinal functions. These and similar results led Berson[8] and others to try to halt or slow down the rate of progression of human retinitis pigmentosa by patching one eye and thus greatly reducing the intensity of the light reaching the eye. However, Berson[9] recently reported no evidence to substantiate that light deprivation with sun glasses or opaque contact lenses will modify the rate of progression of retinitis pigmentosa. The reason of the failure might be that the protected eyes were not totally occluded but easily perceived the diurnal changes in light intensity caused by day and night. The shedding of rod outer segments which must then be phagocytised by the pigment epithelium is normally, at least in certain animals, precipitated by the daybreak in a diurnal rhythm, even if a certain rhythm is preserved in total darkness.

A slowing of the degeneration by rearing the dystropic rats in total darkness was observed by Dowling and Sidman.[5] In that and similar studies

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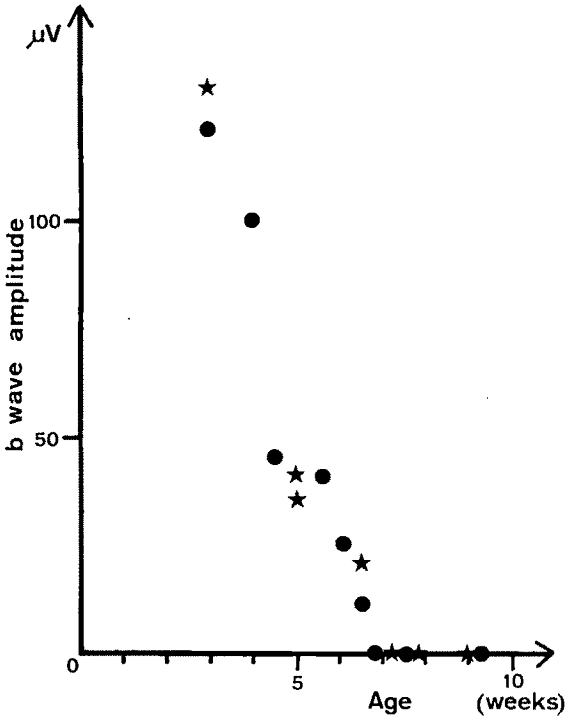

Fig. 1 *The development of the retinal degeneration of young RCS rats as mirrored by the disappearance of the b wave of the ERG. Each dot represents an animal raised in an artificial diurnal rhythm of 2 h darkness/2 h light. Each star represents an animal reared in an artificial cycle of 24 h darkness/24 h light.*

both the total amount of light exposure and at the same time the frequency of light changes were varied in different animal groups. The author considered it of interest to study further the effects of light/darkness rhythms on the rate of decline of retinal function as measured by the electroretinogram (ERG) and to seek to isolate the effects of the diurnal rhythm itself. If the light intensity of the artificial day periods and the total time of light exposure for the lifetime of the animals are kept constant in different series of experiments but the frequencies of the artificial day/night cycles are different in each series, the possible influence on the disease of the light–dark–light changes themselves can be tested.

The present study concerns the effects of artificially hastened and slowed diurnal light rhythms on the rate of degeneration of the retina in RCS rats as mirrored by the ERG.

Materials and methods

The 20 RCS rats of this study were pink-eyed beige-hooded animals. Similarly pigmented animals, congenic with the RCS rats except for the retinal degeneration gene, served as controls. Cannibalism and neglect of the young rats by their mothers lead to the loss of several litters of animals. Some rats (RCS and controls) were housed from birth in a separate room with a 2 hours light (200 lux from an ordinary light bulb)/2 hours darkness cycle monitored by an electric timer. Others were exposed to a 24 hours light/24 hours darkness cycle.

Before ERG recordings were made the rats were dark adapted for 2 h. They were anaesthetised with sodium pentobarbital (40 mg/kg body weight intraperitoneally). Their pupils were dilated with atropine given topically, and the eyelids were held apart with fine sutures. Sometimes a canthotomy had to be performed to eliminate contact between the recording electrode and the lids. The preparation of the animals (the application of a recording platinium electrode on the cornea of one eye, a reference platina electrode on one ear, and a ground electrode on the back of the animal etc.) was carried out in a very dim red light before dark adaptation. Stimulus intensity about 60 lux and stimulus duration 40 ms and sometimes 1 s were provided through a halogen lamp, neutral filters, an electromagnetic shutter, and fibre optics. ERGs were recorded from animals aged between 3 and 10 weeks. A few controls were followed up for four months. Each animal was used in only one recording and subsequently killed. The b wave was measured from the trough of the a wave to the peak of the b wave.

Results

A normal ERG with prominent a, b, and c waves was found in control animals. When reared in ordinary flourescent light (400 lux) (12 h light/12 h darkness) a light-induced degeneration occurred in the control rats with a very low ERG response after about four months.

Control rats subject to 200 lux light from an ordinary light bulb did not show a decreased ERG after two months whether reared under 2 h light/2 h darkness or 24 h light/24 h darkness cycles.

RCS rats subjected to 2 h light/2 h darkness or 24 h light/24 h darkness conditions showed a progressive retinal degeneration leading to an unrecordable ERG after between 7 and 8 weeks of age. Only a and b waves were recorded because of some difficulty in obtaining reliable recordings of the non-existent or very low c waves of the young RCS rats living in the above light conditions. The development of the retinal damage of 16 RCS rats provoked by the two diurnal rhythms as mirrored by the b waves of the ERG is seen in Fig. 1. No substantial difference between the groups in the rate of progression of this illness could be demonstrated. Before the exact time of disappearance of the ERG was known four animals not shown in Fig. 1 were studied after eight weeks of age. They had no recordable ERG response.

Discussion

One must be very careful when comparing the findings of the present study with the results of others, since the RCS strains may differ among laboratories. Considerable differences in light sensitivity between RCS rats of varying degrees of pigmentation were recently reported by LaVail.[10] Strongly pigmented RCS rats showed less difference in disease progression than lightly pigmented RCS animals (such as our pink-eyed variety) when reared in continuous darkness compared with a life under ordinary diurnal light changes. The b wave of our rats never reached the maximum value (600 μV) reported in the study of Kaitz and Auerbach.[7] The explanation might be slightly different RCS strains or different experimental and laboratory conditions. The important point is that there occurred a fast predictable degeneration in our RCS rats with an unrecordable ERG after 7–8 weeks and that laboratory and experimental conditions were identical for all rats (all from the same strain) except for the difference in frequency between the artificial diurnal rhythms.

Cannibalism and neglect of the young rats by their mothers have slowed the progress of the experiments at times. To conserve a necessary number of rats (only one rat was used in each recording) it was necessary to investigate some litters only in the last weeks before the ERG was extinct. Such erratic behaviour in these strains of rats sometimes happens, but the cause is unknown.[10]

A recent report[10] shows that light deprivation, which slows the disease in pink-eyed rats, has no protecting effect on dark pigmented RCS rats. This leads to the conclusion that the suggested therapy of light deprivation for retinitis pigmentosa patients proposed by Berson[8] must be viewed with less optimism. The suggestion was based on the assumption that human retinitis pigmentosa might be caused by a similar defect in pigment epithelial phagocytic capability. However, this theory is not at present considered to be the most likely. Instead a defect in cyclic guanosine monophosphate (GMP) metabolism is now considered to be more probable. On the other hand a large number of various hereditary diseases affect the retina, and it cannot be excluded that some of them are related to defective phagocytosis.

It is well known that profound changes occur in the eye in response to lasting changes in illumination. Rod outer segments are shed at daybreak, at least in certain animals. The retina and pigment epithelium react with long-lasting 2-hour oscillations in the standing potential of the eye in response to changes in the level of adaptation. It therefore did not seem unlikely that artificially hastened diurnal rhythms would constitute an extra stress factor to the diseased RCS rats with their known defect in the phagocytosis of rod outer segments (see above). However, the present study indicates that the frequency of diurnal rhythms does not seem to influence the progression of the disease in pink-eyed RCS rats. It further lessens the hope that continuous efficient patching of one eye of patients with retinitis pigmentosa or other hereditary degenerative fundal diseases, so that less diurnal illumination changes are perceived, will retard the disease.

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References

1 Keeler CE. The inheritance of a retinal abnormality in white mice. *Proc Natl Acad Sci USA* 1924; **10:** 329–33.
2 Bourne MC, Campbell DA, Tansley K. Hereditary degeneration of the rat retina. *Br J Ophthalmol* 1938; **22:** 613–23.
3 LaVail MM. (1979): The retinal pigment epithelium in mice and rats with inherited retinal degeneration. In: Zinn KM, Marmor MF, eds. *The retinal pigment epithelium*. Cambridge, Mass: Harvard University Press, 357–80.
4 Herron WL, Riegel BW, Myers, OE, Rubin ML. Retinal dystrophy in the rat – a pigment epithelial disease. *Invest Ophthalmol Visual Sci* 1969; **8:** 595–604.
5 Dowling JE, Sidman RL. Inherited retinal dystrophy in the rat. *J Cell Biol* 1962; **14:** 73–109.
6 LaVail MM, Battelle B-A. Influence of eye pigmentation and light deprivation on inherited retinal dystrophy in the rat. *Exp Eye Res* 1975; **21:** 167–92.
7 Kaitz M, Auerbach E. Retinal degeneration in RCS rats raised under ambient light levels. *Vision Res* 1979; **19:** 79–81.
8 Berson EL. Light deprivation for early retinitis pigmentosa. A hypothesis. *Arch Ophthalmol* 1971; **85:** 521–9.
9 Berson EL. Light deprivation and retinitis pigmentosa. *Vision Res* 1980; **20:** 1179–84.
10 LaVail MM. Interaction of environmental light and eye pigmentation with retinal degeneration. *Vision Res* 1980; **20:** 1173–7.

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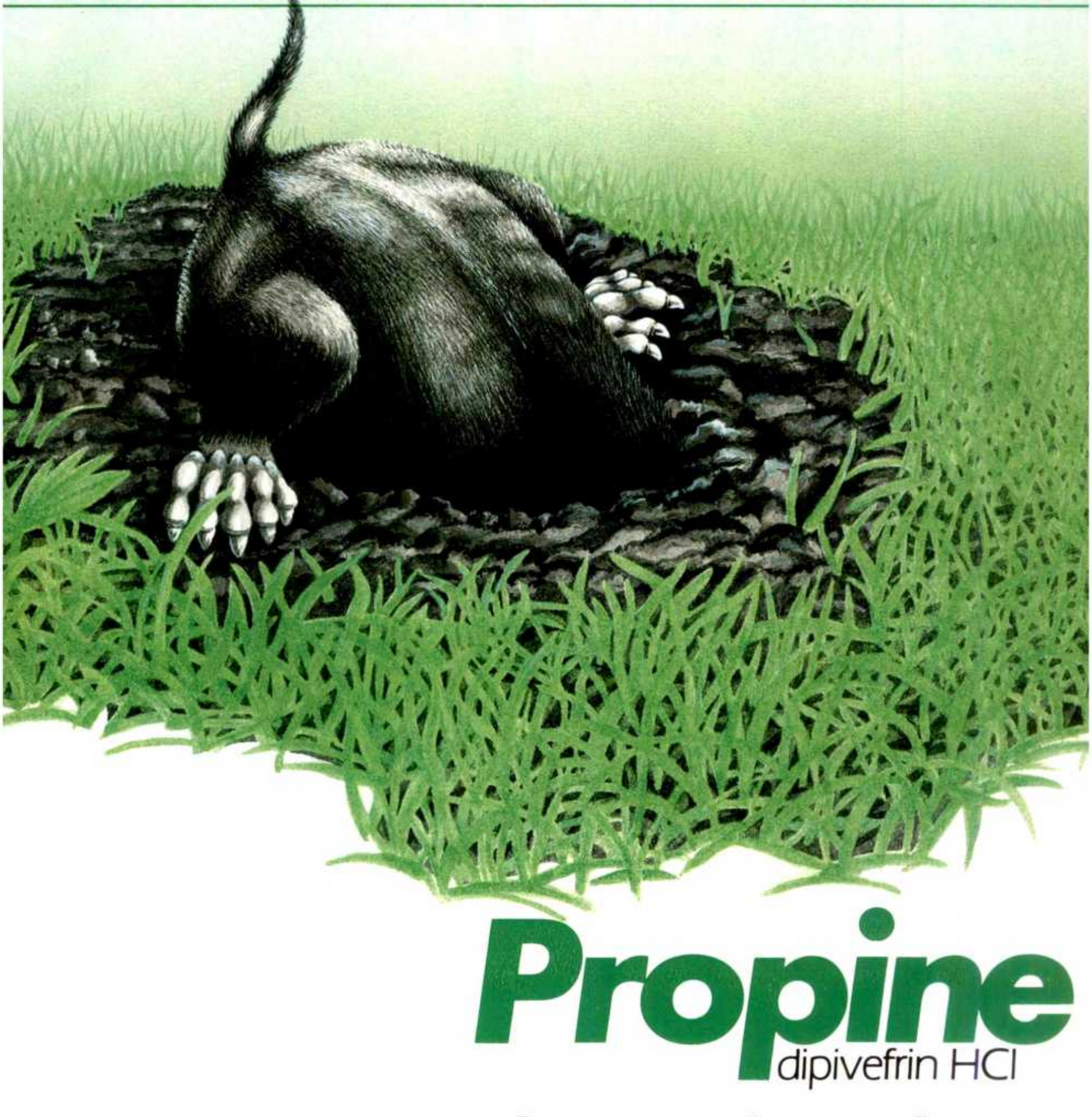

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British Journal of Ophthalmology, 1985, **69**, 471–473

Ankyloblepharon filiforme adnatum in trisomy 18 (Edwards's syndrome)

D I CLARK AND A PATTERSON

From St Paul's Eye Hospital, Old Hall Street, Liverpool L3 9PF

SUMMARY Orbital and ocular abnormalities are commonly found in trisomy 18 (Edwards's syndrome). We believe this to be the first case reported in the literature of ankyloblepharon filiforme adnatum (AFA) occurring in Edwards's syndrome, and the literature on AFA is reviewed.

Ankyloblepharon per se describes direct fusion of the lids usually at the lateral canthus and may be congenital or acquired. Ankyloblepharon filiforme adnatum (AFA), however, is a rare congenital abnormality, first described by Von Hasner in 1881,[1] in which single or multiple strands of fine connective tissue join the upper and lower lids anywhere along the lid but never at the lateral or medial canthus.[2] These strands are extensile, and by forcibly opening the lids their length can be almost doubled.[3] The tissue invariably arises from the 'grey line', anterior to the meibomian gland orifices and posterior to the cilia.[4]

AFA has mainly been reported in association with cleft palate and hare lip,[5] but it has also been described in a wide spectrum of other congenital abnormalities: hydrocephalus, meningomyelocele, and imperforate anus,[6] bilateral syndactyly,[7] patent ductus arteriosus,[8] ventricular septal defect,[9] and in association with ectodermal syndromes.[10 11] It usually occurs as a bilateral condition but has been reported as unilateral in a baby with cleft palate.[12] Furthermore it has been described as an isolated finding in identical twins.[13] The lid abnormalities reported in trisomy 18 (Edwards's syndrome) are numerous, the most commonly found anomalies being narrow palpebral fissure,[14] ptosis, and epicanthus.[14 15] Also described are mongoloid or antimongoloid palpebral fissures,[15] inability to close the lids,[16] blepharophimosis,[14] abnormally long or sparse eyelashes,[15 17] and abnormally thick lids.[16] Harley[18] mentions lid adhesions (that is, ankyloblepharon) as a rare event in trisomy 18, but this is the first report of AFA associated with this syndrome.

Case report

A 5 lb 12 oz (2·6 kg), white female was born at 39 weeks gestation to a 22-year-old primigravida. The pregnancy was normal and the mother had not taken drugs or been exposed to *x* rays. There was no family history of congenital abnormalities and no consanguinity. The baby had many abnormal features which were consistent with diagnosis of trisomy 18, confirmed by chromosomal studies.

The clinical features of note were micrognathia, high arch palate, low set ears, and an odd shaped head. There was overriding of the second and third fingers of both hands and the fifth over the fourth finger of the right hand only. The right foot was inverted, and she had rockerbottom feet and short big toes. The head circumference was 34 cm at birth.

The right eyelids were joined by one band of expansile tissue, the left eyelids being joined by two such bands (Fig. 1). Other orbital findings were hypoplastic supraorbital ridges, slight epicanthus, and mongoloid slant. She also had abnormally long eyelashes. There were no obvious corneal or lenticular changes, and funduscopy was normal.

As the bands were in the visual axis they were divided as a matter of urgency. No anaesthetic was necessary and little bleeding occurred.

PROGRESS

At birth the baby was unable to suck and so had to be fed by nasogastric tube. At 6 weeks of age she developed a chest infection and was also found to have an enlarged heart. A two-dimensional electrocardiogram demonstrated a large ventriculoseptal defect. The baby recovered from the chest infection

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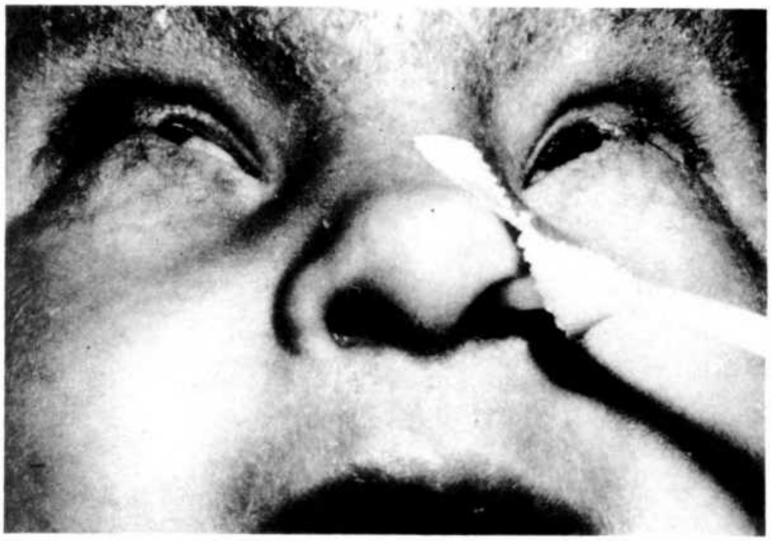

Fig. 1 *Ankyloblepharon filiforme adnatum in patient with trisomy 18.*

and despite the heart abnormalities and feeding difficulties was coping well. However, the ultimate progress is not good, as few of these children live beyond one year.

Discussion

The histology of the connective tissue strands has been shown to consist of a vascularised central core surrounded by stratified squamous epithelium.[19] The aetiology of this abnormality is unknown, and a number of theories have been proposed. Von Hasner thought the lesions were the result of intrauterine inflammation, but this is unlikely for two reasons: firstly, there is no histological evidence of 'inflammation' having occurred, and secondly, despite their close proximity, there is no involvement of the cilia or meibomian glands. Wintersteiner[19] suggested that trauma by the fingernail of the fetus provoked proliferation of mesodermal tissue. However, this has been refuted because the fingernails of a fetus do not reach the ends of the fingers until the late months of gestation long after fusion of the eyelids has occurred.[9] It has also been suggested that partial failure of the eyelids to separate is the cause,[20] but, as the normal temporary eyelid fusion is composed solely of epithelium and complete by the eleventh week of gestation, it is clear that the bands reflect an abnormality in the fusion process and not in separation.

The currently accepted theory is that the condition is due to an interplay of temporary epithelial arrest and rapid mesenchymal proliferation, allowing union of the lids at certain points.[21]

The association of AFA with the ectodermal syndromes would support this theory, as Hay and Wells comment that the syndrome of AFA, ectodermal defects, and cleft lip and palate could be explained by a 'defective interaction of ectoderm and mesoderm, probably a fault in mesodermal tissues' ability to organize ectoderm.'[10]

It has been postulated[22] that in trisomy 18 there is abnormal cellular proliferation and hyperplasia which, if applied to the relationship of mesoderm and ectoderm on the lid margin, may have caused the abnormal strands and lend further weight to the theory of Judge *et al.*[21]

It has been postulated[7] that many cases of AFA are part of the popliteal pterygium syndrome (PPS), comprising cleft lip-palate, popliteal and intercrural pterygia, digital and genital anomalies, and AFA. However, this is unlikely, because despite the variable expressivity of the PPS, AFA occurred only in 3 out of 29 cases presented by Gorlin *et al.*[11]

In 1980 Rosenman *et al.*[5] divided AFA into four subgroups (Table 1) and indicated that groups I and II were sporadic and groups III and IV were autosomal dominant with variable expressivity. It is not possible to be certain whether our case falls into one of these subgroups or should be placed in a new

Table 1 *Classification of ankyloblepharon filiforme adnatum*

Group	*Associated abnormalities*
I	None
II	Cardiac or central nervous system
III	Ectodermal syndrome
IV	Cleft lip and/or palate

subgroup V of AFA and chromosomal abnormalities. It could be included in group II from the cardiac defect or in group IV, as 15% of trisomy 18 have cleft palate.[23]

We thank Miss Elizabeth A Wreyford and Miss Gillian Doherty for typing the manuscript, and Mr C Mody for photographic assistance.

The chromosomal studies were carried out at the Cytogenetic Laboratory, the Royal Liverpool Hospital.

References

1 Von Hasner. Ankyloblepharon filiforme adnatum. *Z Heilkd* 1881; **2:** 429.

2 Duke-Elder S. *System of ophthalmology*. London· Kimpton, 1964; **3:** 869–71.

3 Weill S. *Arch Auken Heilk* 1908; **59:** 278. Cited by Duke-Elder S. *System of ophthalmology*. London: Kimpton, 1964; **3:** 869.

4 Khanna VN. Ankyloblepharon filiforme adnatum, *Am J Ophthalmol* 1957; **43:** 774–7.

5 Rosenman Y, Ronen S, Eidelman AI, Schimmel MS. Ankyloblepharon filiforme adnatum. *Am J Dis Child* 1980; **134:** 751–3.

6 Kayarian EL, Goldstein P. Ankyloblepharon filiforme adnatum with hydrocephalus, meningocele and imperforate anus. *Am J Ophthalmol* 1977; **84:** 355–7.

7 Akkermans C, Stern LM. Ankyloblepharon filiforme adnatum. *Br J Ophthalmol* 1979; **63:** 129–31.

8 Lobstein A, Haarscher A. Ankyloblepharon filiforme congénital et malformation cardiaque associée. *Bull Soc Ophtal Mol Fr* 1953; **2:** 128–31.

9 Rogers JW. Ankyloblepharon filiforme adnatum. *Arch Ophthalmol* 1961; **65:** 114–7.

10 Hay RJ, Wells RS. The syndrome of ankyloblepharon, ectodermal defects and cleft lip and palate: an autosomal dominant condition. *Br J Dermatol* 1976; **94:** 277–89.

11 Gorlin RJ, Sedano HO, Cervenka J. Popliteal pterygium syndrome. *Pediatrics* 1968; **41:** 503–9.

12 Kapoor MS, Sood GC, Aurora AL, Kapoor S. Unilateral ankyloblepharon filiforme adnatum. *Indian J Ophthalmol* 1977; **25:** 43–4.

13 Howe J, Harcourt B. Ankyloblepharon filiforme adnatum affecting identical twins. *Br J Ophthalmol* 1974; **58:** 630–2.

14 Howard RO. Classification of chromosomal eye syndrome. *Int Ophthalmol* 1981; **4:** 77–91.

15 Ginsberg J, Perrin E, Sueoka W. Ocular manifestation of trisomy 18. *Am J Ophthalmol* 1968; **66:** 59–67.

16 Calderstone JP, Cliess J, Borodic G, Albert D. Intraocular pathology of trisomy 18. *Br J Ophthalmol* 1983; **67:** 162–9.

17 Weber WW, Mamvness P, Day R, Miller P. Trisomy 17–18 studies in longterm survival. *Pediatrics* 1964; **14:** 533–41.

18 Harley RD. *Pediatric ophthalmology*. Philadelphia: Saunders, 1983.

19 Wintersteiner H (1908). Ein neuer Fall von Ankyloblepharon filiforme. *Arch Augenheilkd* 1908; **59:** 196.

20 Mattson R. Ankyloblepharon filiforme adnatum. *Acta Ophthalmol (Kbh)* 1950; **28:** 223–7.

21 Judge H, Mott W, Gabriels J. Ankyloblepharon filiforme adnatum. *Arch Ophthalmol* 1929; **2:** 702–8.

22 Ginsberg J, Bove K, Nelson R, Englander GS. Ocular pathology of trisomy 18. *Ann Ophthalmol* 1971; **3:** 273–9.

23 Gorlin RJ, Cervenda J, Prugansky S. *Birth Defects* 1971; **7:** 25.

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Book reviews

Animal Models of Ocular Diseases. Eds. KHALID F TABBARA AND ROBERT M CELLO. Pp. 285. US$39·75. Charles C Thomas: Springfield, Illinois. 1984.

Not quite a report of conference proceedings but near enough, this is the outcome of a seminar sponsored by the Alta California Eye Research Foundation, and it attracts at least one of the criticisms to which that type of compilation is prone—variability of approach. Thus some of the contributions are straightforward descriptions of experiments designed to unravel a specific problem: as such they might more easily have been submitted for publication in a scientific journal. That is not to doubt the intrinsic worth of the articles but to question their appropriateness in a book with a title that implies an emphasis on the choice and use of animal models rather than on disease entities themselves. Fortunately this type of chapter is in the minority, and for the most part the authors provide valuable overviews of the relevance of animal models in a variety of ocular disorders, whether experimentally induced or naturally occurring, to the human situation.

After a helpful introduction to the principles to be observed in selecting animals for research the book is divided into four sections. The first deals with infectious diseases, covering herpetic and chlamydial infections, a variety of bacterial disorders including leprosy, and toxoplasmosis. The second section concerns neoplastic diseases but is restricted to extraocular tumours, and it is to be regretted that there is no mention of animal models of uveal melanoma and retinoblastoma. A miscellany of disorders, chiefly metabolic, are covered in the third section, while the final part of the book describes a number of immunological conditions, with emphasis on those in which the ocular signs are part of a broader systemic process.

There is much useful information here for the investigator, and, despite some reservations, the book is one which should find a place in any centre concerned with experimental research into ocular disease. A GARNER

Pediatric Ophthalmology Practice. 2nd edn. By EUGENE M HELVESTON AND FORREST D ELLIS. Pp. 361. No price given. Mosby: Toronto. 1984.

In the foreword to this text, by Dr Marshall M Parks, reference is made not only to Costenbader, the founder of paediatric ophthalmology in the United States, but also to Doggart, who wrote the first text on paediatric ophthalmology published in 1947, and Dr Parks points out that Helveston and Ellis's second edition of this book has many of the good points that Doggart's text had, but in particular that it is coherent. While not pretending to be a comprehensive textbook, it outlines many aspects of eye problems in childhood, and the format is sensibly kept at a practical level and illustrated liberally with photographs and line drawings. The person most likely to benefit most from this book is a resident who is about to start on a paediatric ophthalmology service, but I think it will also continue to be useful to non-ophthalmologists and non-specialist ophthalmologists alike. DAVID TAYLOR

A Colour Atlas of The Eye and Systemic Disease. By ERNA E. KRITZINGER AND BARRY E WRIGHT. Pp. 72. £15·00. Wolfe Medical Publications: London. 1984.

This book presents in a clear and readable form the major abnormalities of the eye associated with common systemic diseases. It also provides excellent colour photographs of all the major eye signs associated with these diseases and which physicians should be able to recognise in their outpatient clinics, even though they may seldom have the opportunity to encounter such patients. Some illustrations are of extremely rare diseases, and the frequent use of eponyms gives rise to some confusion—for example, the Gronblad-Strandberg syndrome, which is apparently a synonym for pseudoxanthoma elasticum. It seems perhaps a little unnecessary to burden the reader with the names of both for the same condition.

Apart from one or two minor inaccuracies (such as that lipaemia retinalis occurs with type II hyperlipidaemia) and one or two important omissions (such as lack of any reference to malignant melanoma of the choroid) I found this an excellent summary of the major medical conditions that are associated with eye disease. It should provide excellent reading for clinicians in such specialties as rheumatology, dermatology, endocrinology, and neurology as well as be of considerable value to postgraduate students in ophthalmology and general medicine who wish to review medical eye disease. D J GALTON

Key Facts in Ophthalmology. By GEORGE W WEINSTEIN, V K RAJU, LARRY SCHWAB, GARY T RAFLO, DAVID E SWANSON. Pp. 344. £22·00. Churchill Livingstone: Edinburgh 1984.

This book is imaginatively set out and is aimed at 'students in ophthalmology and medical practitioners.' It is divided into two main sections: I, core knowledge, and II, psychomotor skills. The text is broken down into simple numbered sentences, the contents of which vary from colloquialisms in some sections to ophthalmic terminology too involved for the uninitiated for whom the book is intended. The text is rather repetitive, and although its five authors are from the same department it lacks editorial leadership. Thus on p. 41 the reader is informed that surgical removal of 'congenital cataract may be indicated as early as age 6 months or deferred.' Fortunately on p. 312 he finds out that congenital cataract should be in fact removed within the first 6 weeks of life. The section on neuro-ophthalmology is very good, though it would have been helpful had some of the basic terms such as relative afferent pupillary defect been explained a little earlier than in the last section of the book. The illustrations consist of clear and detailed line drawings and photographs; the latter may be adequate for illustrating external disorders, but the black-and-white fundus photographs are poor. The reader's irritation is not soothed by his discovering the same example of angioid streaks turned through 180° a few chapters apart, nor by the large number of spelling mistakes.

In all, I do not think that at £22 this paperback offers good value for money, though I can see that it can be useful as a pre-examination revision book for nurses and medical students. Z GREGOR

Binocular Vision Anomalies: Investigation and Treatment. By David Pickwell. Pp. 178. £17·50. Butterworths: Sevenoaks, Kent. 1984.

The author is a professor of optometry at Bradford University, and this book is intended for students and practitioners of optometry. Accordingly, there is greater emphasis on spectacles and exercises for the treatment of binocular anomalies than might be found in a medical or orthoptic text. There are a number of points that I disagree with in the text.

In chapter 1 the author states that cyclophoria can occur on dissociation. There is no evidence that this occurs, and in fact the author retracts the statement later in the text. In chapter 2 the fact that the eye behind the occluder may move in latent squint does not contravene Hering's law, which applies to conjugate gaze efforts only. Although the Hirschberg test is described, the much more accurate prism reflection test (Krimsky test) is not. In general, the section on measurement of angle of squint is sketchy.

In chapter 3 for some reason the prism and alternate cover test is not mentioned in the section on measurement of degree of heterophoria, despite its ease, accuracy, and universal use. In chapter 4, on prism relief of heterophoria, the use of Fresnel membrane prisms for temporary relief and for discovering the optimum correction is not described. In chapter 5 the striking claim is made that patients who work in stuffy atmospheres develop anoxaemia, which causes divergence weakness exophoria. The association of divergence weakness with raised intracranial pressure is not mentioned. I can find no reference to the use of miotics in convergence excess esodeviations. In chapter 6 it is implied that distinguishing between true and simulated divergence excess exodeviation is unimportant. Accordingly a distance cover test and measurement of AC/A ratio are not mentioned. In general the importance of the AC/A ratio in latent, and manifest horizontal deviations is surprisingly neglected. In chapter 7, on hyperphoria, nothing is said on compensatory head tilting (including examination of the family photograph album) or on the Bielschowsky head-tilt test. Dissociated vertical deviation *is* treatable surgically, with reasonable if not excellent results.

Chapter 11, on amblyopia, presents the now rather obsolete classification of 'amblyopia of arrest' and 'amblyopia of extinction,' based on a very misleading concept of infant visual acuity. 'Amblyopia ex anopsia' is preferred as a term to the much clearer 'simulus-deprivation amblyopia,' and bilateral ametropic amblyopia, as in high hypermetropia, is not mentioned, though meridional amblyopia is. It is recommended that children should be tested for visual acuity of the worse eye first to avoid memorising the letter chart. It should be remembered that some children regard the letter chart as a test, and are probably best encouraged by using the better eye first, with a fresh chart for the other eye.

In the treatment of amblyopia full-time occlusion is recommended, with part-time occlusion if this is impracticable. Current orthoptic practice, in Great Britain and elsewhere, regards part-time occlusion as at least as effective as full time treatment and much less likely to lead to problems. It is suggested that amblyopia can be treated by teaching awareness of physiological diplopia. I am sceptical about this.

In chapter 13 the traditional and never-explained 'tonus' allowance in cycloplegic refraction appears. There seems to be no sense in continuing this tradition if the object of convex lenses in esotropia is relaxation of accommodation. It is implied that consecutive exotropia is caused by giving glasses to hypermetropic patients who were operated on as children. Chapter 15 concerns examination of young children. Table 15.1 perpetuates the hoary old idea that a child can see no better than 6/36 at 1 year and 6/12 at 2 years. This has been conclusively disproved by preferential looking tests of acuity. In the description of nystagmus blockage syndrome (p. 146), the head turn is the wrong way. In chapter 16 investigation of inconcomitant deviations is considered. Obviously only guidelines are being given here, but a simple guide such as the Parks's three-step test would aid understanding of how to elicit the responsible vertical paretic muscle. The vital fact that *all* third nerve palsies with pupils affected are potentially aneurysmal is not mentioned, and should be. Traumatic fourth nerve palsies are not due to direct trochlear trauma as a rule. Again the role of Fresnel prisms is not covered in the section on management. In chapter 17 it is implied that 'miners' nystagmus' is still seen in mining areas. It is, but only because some individuals learn how to cause it voluntarily in order to gain compensation.

Overall, the role of surgery is underplayed and is consistently said to be inaccurate. With newer techniques such as adjustable sutures and botulinus toxin, this is no longer the case. In summary, although the book may well have a place in the optometry curriculum, it is not of value for ophthalmologists in training.

J P LEE

Diagnostic Diagrams: Ophthalmology. By Andrew P Schachat and Alan F Cruess. Pp. 124. £10·00. Williams and Wilkins: London. 1984.

The authors, in their foreword, realise the significant increase in material which the medical student has to assimilate, and their book is an attempt to make the assimilation of ophthalmology easier. They then provide a suggested reading list of 19 comprehensive books and articles and a slide collection of clinical photographs which rather negates the purpose of a simple book for medical students. The interested student very quickly finds further reading from his teachers; the rest require one simple readable book for their short time in ophthalmology.

The book is illustrated throughout in black-and-white and consists of text and diagnostic diagrams which lead to diagnosis of certain groups of symptoms and signs. In this manner, by describing the relevance of symptoms and signs and their elicitation, each chapter progresses to a diagnostic diagram. Visual loss, the red eye, anisoconia, visual field defects, strabismus, leucoconia, glaucoma, diplopia, proptosis, headache, and ocular emergencies are each treated in this way in turn. This type of diagnostic diagram is at present having a certain fashion in medical student teaching but is after all what all students have been doing informally for many years. It is a good way of revising and testing one's own knowledge, but whether it is beneficial as the formal basis of a textbook is open to question.

There is probably too much complicating detail for most medical students, and the lack of colour illustrations takes away much of the value of several chapters. Ophthalmology par excellence requires colour illustration, and much of the careful text loses its point without colour, for example, in describing 'red' lesions in the retina with a black-and-white fundus photograph. It is also very unsatisfactory for the medical student not to have any simple details of treatment when required. Students have a good knowledge of pharmacology and not even to mention simple antibiotic eye drops in the treatment of conjunctivitis is a remarkable omission. Altogether this is a new book which has not really come off, and it would leave the medical student feeling there were too many loose ends not tied up, especially with regard to simple treatments. JAMES L KENNERLEY BANKES

Visual Disorders in the Handicapped Child. By JOHN L GOBLE. Pp. 287, SFr. 127·00. Marcel Dekker: New York. 1984.

This excellent book fulfils everything that it sets out to do. The author aims to help general physicians, paediatricians, and neurologists, but also intends to interest ancillary personnel who deal with handicapped children in understanding their visual disorders. Most of the conditions are explained simply, and there are ample further references for those wishing to look further into the subject.

Although the book is laid out in a logical and compartmented way, the author's experience comes through in the practical and clear manner in which he explains many of the conditions and problems that these children have. There is a good author and subject index. If there are any criticisms it may be that there is not enough detail on practical aspects on helping blind babies and children, or on practical aspects of vision testing by non-ophthalmologists. In spite of these criticisms, however, I think that this is a useful book. DAVID TAYLOR

The Visual System in Myelin Disorders. Eds. A NEETENS, A LOWENTHAL, J J MARTIN. Pp. 518. Dfl 225·00. Junk: The Hague. 1984.

This book has resulted from a long collaboration in Antwerp between an ophthalmologist (A Neetens), a neurochemist (A Lowenthal), and a neuropathologist (J J Martin). A further eight Belgian contributors were invited in addition to 16 American and 24 European contributors, thus producing a truly international book.

The book is subdivided into sections on basic research into normal and abnormal myelin, and the pathophysiology of myelination. The major section and indeed the major part of the book is devoted to human and animal myelin disorders. This section includes a number of distinguished experts discussing the diagnosis and clinical features of demyelination in the afferent visual system and in the ocular motor system. The metabolic disorders from metachromatic dystrophy to Menkes' disease are fully described. Finally there is a short chapter on treatment.

The chapters vary in length, but on the whole the standard is good. This book therefore provides a comprehensive review on myelin and its disorders, but some complex chapters on basic aspects of myelin may frighten many ophthalmologists away. They should, however, avail themselves of the opportunity to browse through this book, for the emergence of nuclear magnetic resonance scans provides an exciting glimpse into the future. They may also obtain stimulating thoughts from other chapters, such as why conjunctival biopsy is used for the diagnosis of neurolipidoses but is not used by ophthalmologists for other diagnostic purposes. M D SANDERS

Notes

Adaptive processes

An international symposium on 'Adaptive processes in visual and oculomotor systems' will be held on 16–20 September 1985 at Asilomar, California, USA. Details from D Zee, Conference cochairman, Department of Neurology, Johns Hopkins Hospital, 600 N Wolfe Street, Baltimore, MD 21205, USA.

Classification of retinopathy of prematurity

An international committee with Professor A Garner (UK) in the chair prepared an 'International classification of retinopathy of prematurity.' This classification was published in the *BJO* last October (*Br J Ophthalmol* 1984; **68:** 690–7). It has also appeared in *Pediatrics* 1984; **74:** 127–33 (July 1984 issue), *Archives of Ophthalmology* 1984; **102:** 1130–4 (August 1984 issue), and *Oftalmolog* 1984; **4:** 13–6 in an edited version. It has been submitted for publication to several other journals likely to reach an audience concerned with the problems it discusses.

Metabolic eye disease

The seventh symposium of the International Society on Metabolic Eye Disease will be held at Parma, Italy, on 11–14 May 1986. Theme: 'Neonatal aspects.' For free communications a topic and 500-word abstract should be sent before 1 November 1985 to Heskel M Haddad, MD, Program Chairman, 1125 Park Avenue, New York, NY 10128, USA.

Correction

In the article entitled 'Contrast sensitivity and visual disability in chronic simple glaucoma' by J E Ross, A J Bron, and D D Clarke (*Br J Ophthalmol* 1984; **68:** 821–7) an error occurred in Table 2. The degrees of freedom referred to an analysis of variance, and in each case the figure 1 should have been separated from the subsequent three figures as follows: 1, 184; 1, 204; 1, 210; 1, 141; 1, 106; 1, 113; 1, 101; 1, 104.

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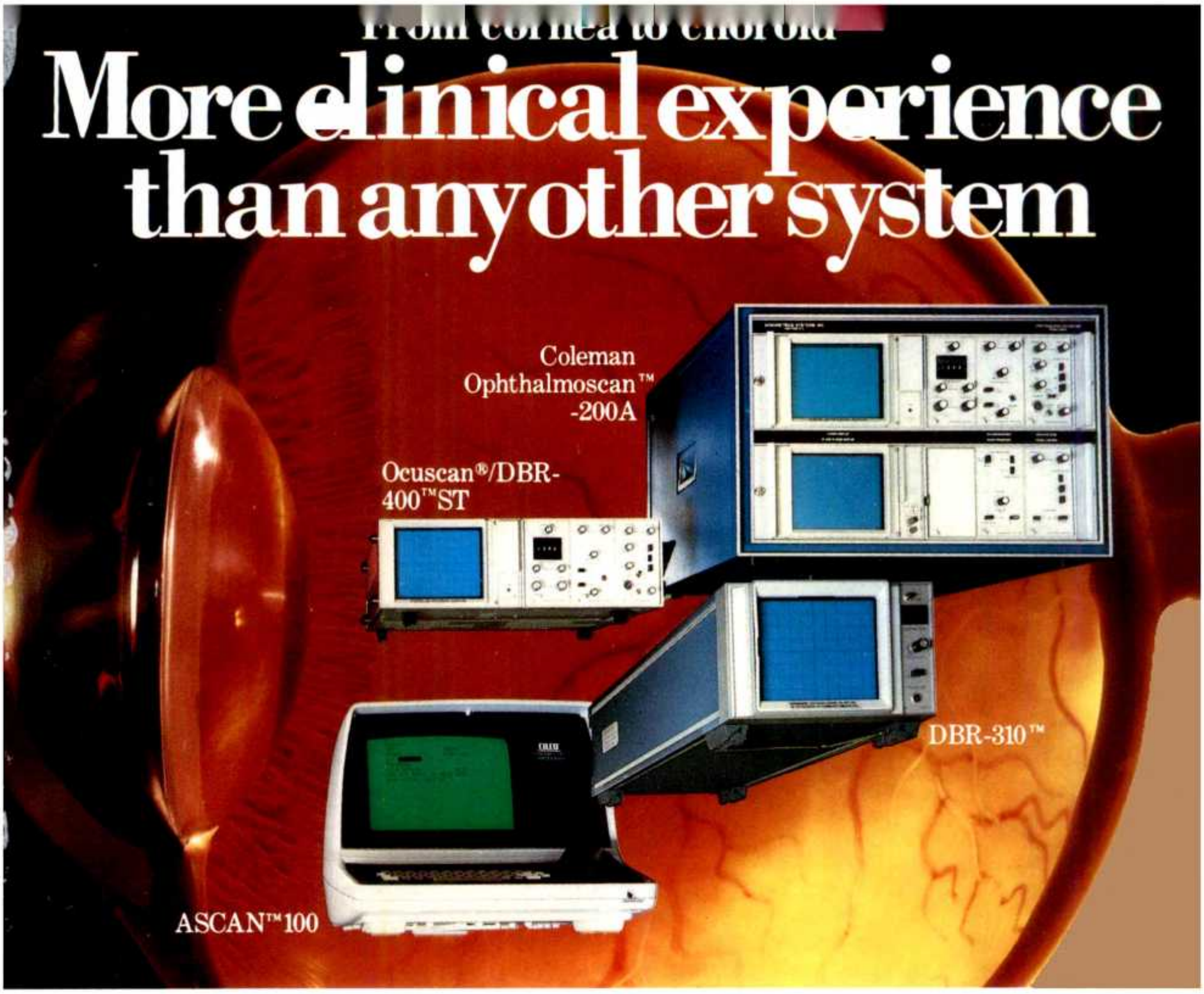
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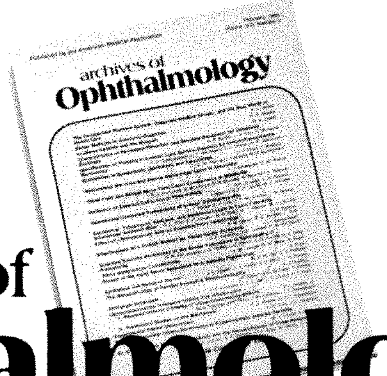

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